THE American Journal OF Gastroenterology

VOL. 31, NO. 6 JUNE, 1959

Twenty-fourth Annual Convention
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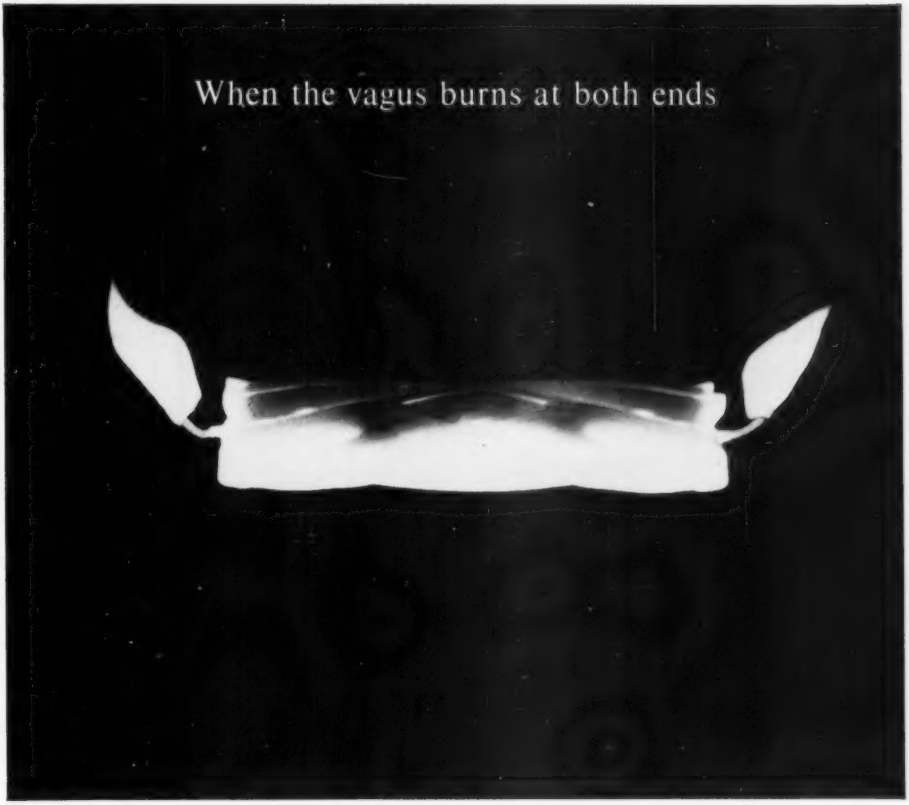
1. Breidenbach, L., and Secor, S. M.: Proper Handling of the Colostomy Patient, Amer. J. Surg. 93:50, 1957.



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THE American Journal OF Gastroenterology

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contents:

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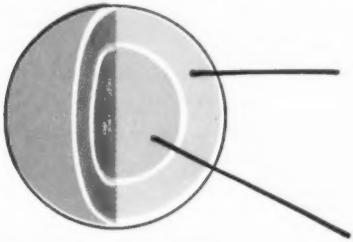

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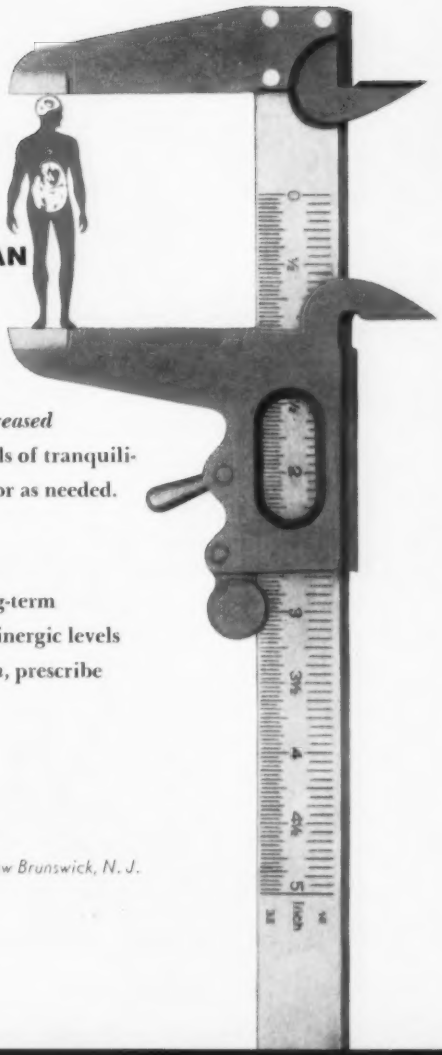

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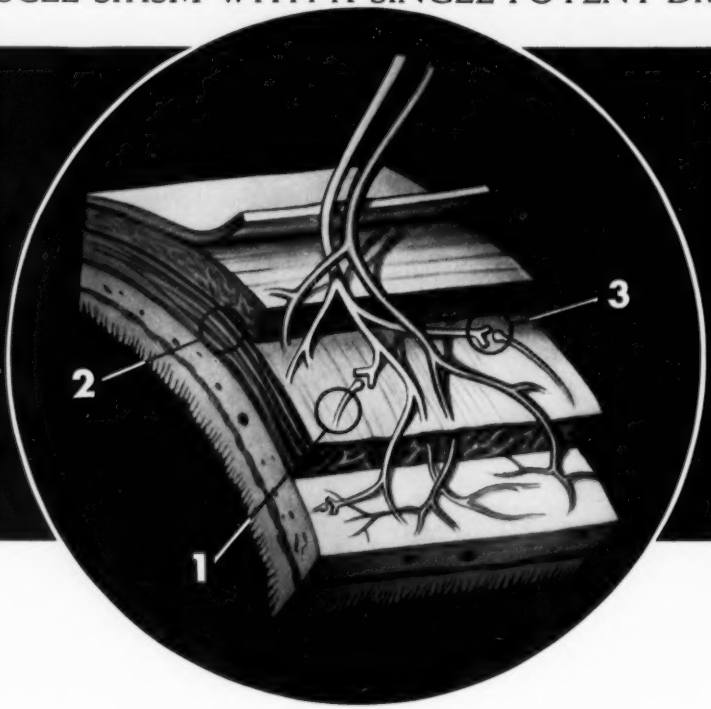

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1. Holbrook, A. A.: Report abstracted in M. Science 4:46 (July 10) 1958. 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955. 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955. 4. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.

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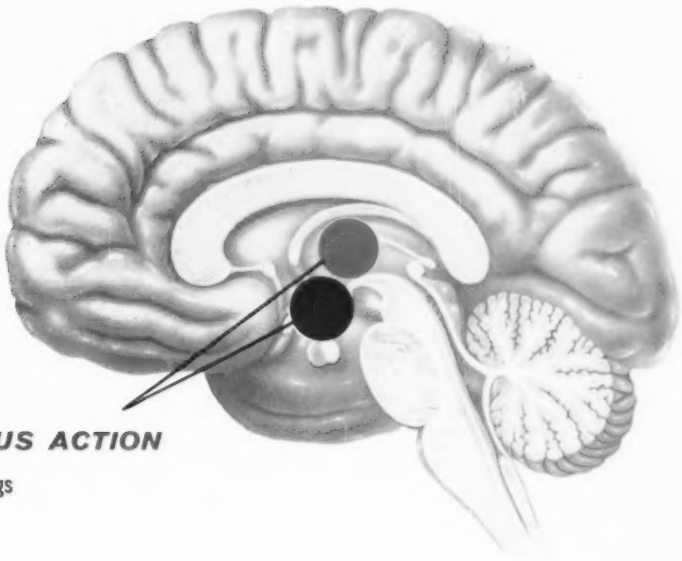

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1. Leavitt, J. M.: Scientific Exhibit, Annual Meeting of the New York State Medical Society, New York, N. Y. May 12-16, 1958.

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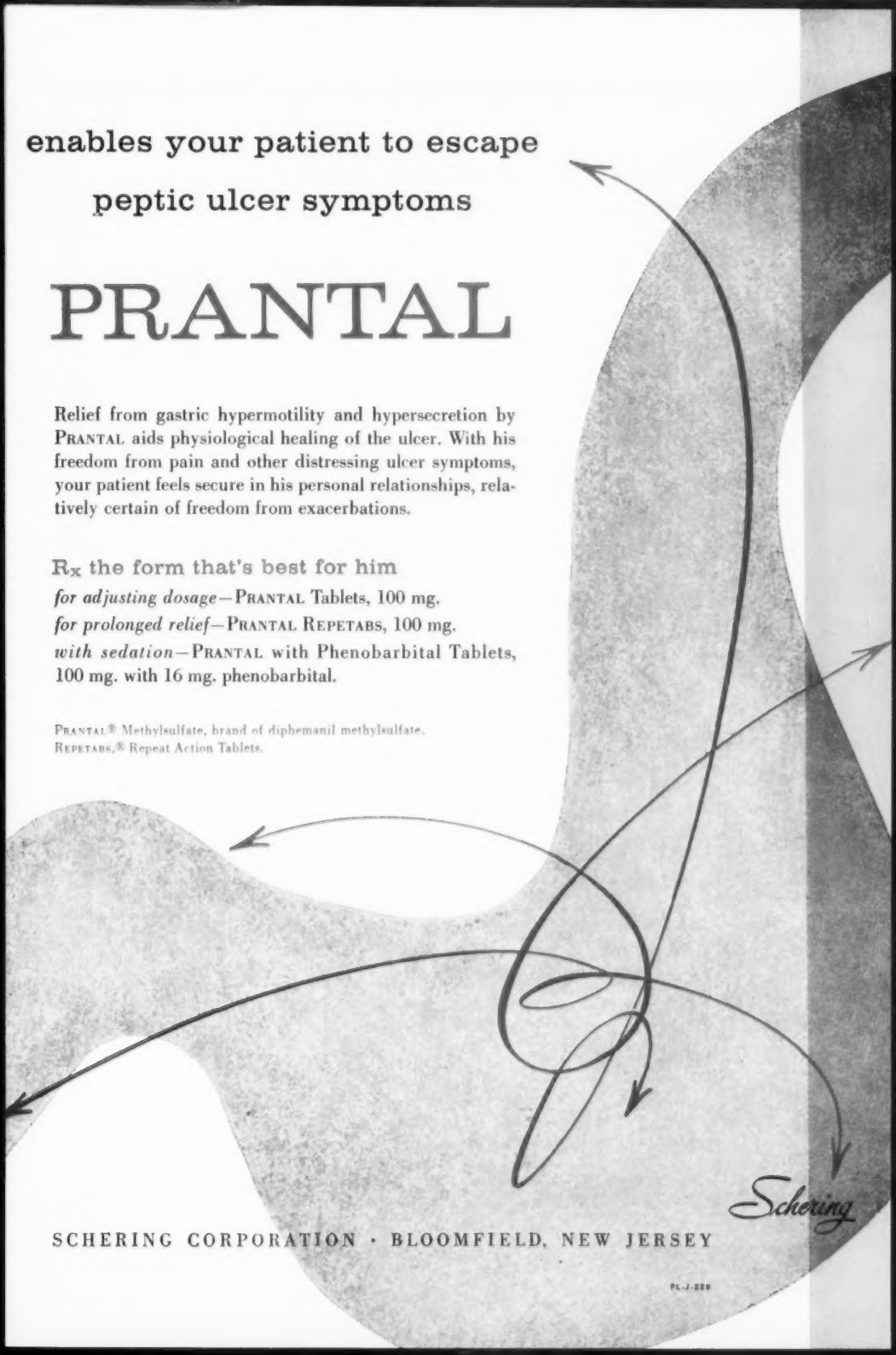

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THE American Journal OF Gastroenterology

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VOLUME 31 JUNE, 1959 NUMBER 6

PANEL DISCUSSION ON STEROIDS IN GASTROENTEROLOGY*

MURREL H. KAPLAN, A.B., M.D., F.A.C.G., *Moderator*†

FREDERICK FITZHERBERT BOYCE, B.S., M.D.‡

PAUL M. HYDE, B.S., M.S., Ph.D.¶

ALBERT SEGALOFF, B.S., M.S., M.D.§

and

FLOYD R. SKELTON, M.D., Ph.D.#

New Orleans, La.

Dr. Murrel H. Kaplan:—Fellow Members of the College and Guests:

Since the introduction of steroids in the treatment of rheumatoid arthritis by Dr. Hench in 1951, these hormones have been tried by every branch of medicine. We in gastroenterology have likewise followed. Of course, there have been many uses, many misuses, and of course, many abuses. This morning, we hope to crystallize the prevailing thoughts on this broad subject, as well as to offer some of the basic physiologic principles involved.

We are fortunate to have with us a few of New Orleans' outstanding basic scientists to help clarify some of the issues.

I should like to encourage the floor to submit as many questions as possible. In order to stimulate this, we have asked each of the panelists to submit a few minutes of didactic information.

First, I should like to introduce on my far right Dr. Albert Segaloff, endocrinologist, research investigator, clinician, the Director of Endocrinology at the Alton Ochsner Medical Foundation, and Associate Professor of Clinical Medicine at Tulane.

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*Presented before the 23rd Annual Convention of the American College of Gastroenterology, New Orleans, La. 20, 21, 22 October 1958.

†Chief, Department of Gastroenterology, Touro Infirmary.

‡Professor of Clinical Surgery, Tulane University School of Medicine.

¶Assistant Professor of Biochemistry, Louisiana State University School of Medicine.

§Associate Professor of Clinical Medicine, Tulane University School of Medicine.

#Associate Professor of Pathology, Louisiana State University School of Medicine.

On my immediate right is Dr. Paul M. Hyde, recently from Dr. Williams' laboratory in Washington; previously he had trained with Dr. Doisy in St. Louis. Dr. Hyde is Steroid Chemist of the Urban Maes Research Foundation, and Assistant Professor of Biochemistry at Louisana State University.

On my left is Dr. Floyd R. Skelton, a Canadian import, who received his early training with Dr. Hans Selye. He is an endocrinologist and pathologist. Floyd is best known, I think, for his work on experimental adrenal regeneration hypertension. Dr. Skelton is Director of Research at the Urban Maes Research Foundation, and Associate Professor of Pathology at Louisiana State University.

On my far left is Dr. Frederick Fitzherbert Boyce, Clinical Professor of Surgery at Tulane; author of several books, one of which is "Regional Enteritis". Several years ago Dr. Boyce was awarded the Gross prize for his work on the liver in surgery.

Dr. Segaloff will start with his discussion.

Dr. Albert Segaloff:—The adrenal is scarcely an independent organ, despite the fact that it produces steroids which are necessary to life, and in many regards, to happiness, since the adrenal steroids support such a large segment of the medical and chemical population.

The adrenal depends upon the pituitary both for its basic function and probably for its response in various conditions which are now popularly called "stressful". The inter-relationships between the pituitary and the adrenal are often referred to as the pituitary adrenal axis, and in man the pituitary mediates its position, by the secretion of ACTH. You must, however, remember that, like the overlapping in steroid functions, there is a distinct overlap in the functions of the pituitary, and the melanocyte stimulating hormone has ACTH activity which contributes a not inconsequential part to the picture.

When you administer ACTH as a therapeutic agent, you make the adrenal produce steroids; on the other hand, when you administer steroids, you inhibit the pituitary secretion of ACTH and thereby decrease the endogenous steroid production.

In the normal state, ACTH and the production of Compound F and Compound B are in balance. Remember, these are the two major steroids produced in man which do affect the ACTH excretion. If you take the brakes off by taking out the adrenal, there is a marked increase in ACTH and there is nothing to inhibit the pituitary.

If you take an adrenalectomized individual and give him a hydrocortisone, or cortisone, or other active corticosteroids, the increased ACTH will be reduced to normal or subnormal levels. If you remove the pituitary, the ACTH is removed, the secretion of corticosterone and hydrocortisone is markedly re-

duced but doesn't disappear. The individual can often get along except in stressful situations without additional corticosteroids.

This all looks very nice except we now know too much to believe this is the only picture.

I think we can clarify some of the additional points. As many of you know, there is an additional corticosteroid, aldosterone, which does not inhibit the pituitary excretion of ACTH, nor does ACTH influence its production.

This steroid, which is of great potency, is under the influence of the sodium potassium ratio or the absolute amount of sodium, and acts independently of the pituitary adrenal axis. On the other hand there are C^{19} androgens which are produced in the adrenal. There is a wealth of evidence now that ACTH will increase the C^{19} androgens being secreted. These C^{19} compounds, however, also do not enter into balance and inhibit ACTH, so that these are by-products which do not keep the pituitary adrenal axis in balance.

So may we reiterate that the administration of ACTH increases the secretion of hydrocortisone, corticosterone and C^{19} androgens but not aldosterone, and decreases secondarily the endogenous secretion of ACTH. On the other hand, if we give corticosteroids, we inhibit the secretion of ACTH directly, the adrenal is reduced in size because of the removal of the trophic effect of ACTH, and there is a reduction in the adrenal production of C^{19} androgens, so that here we have a system which of itself is in balance. Many of the effects of either ACTH or cortical steroids on the gastrointestinal tract and elsewhere are mediated by steroids in general and not by the ACTH.

ACTH, so far as we know, has its sole effect on the adrenal cortex to produce growth and morphologic changes and the secretion of steroids, so that all of the effects of either ACTH or adrenal steroid administration are mediated by the effect of the steroid on the end organ.

One of the major deleterious effects, and I think it is particularly applicable in gastroenterology where we are frequently dealing with long-term administration, is the production of osteoporosis.

Most people, even after prolonged courses of corticosteroids, have their adrenals bounce back and return to normal function, but, on the other hand, some people do not.

Osteoporosis is common to the administration of all the known active corticosteroids, the administration of ACTH, and to the natural disease of hypercorticism, namely, Cushing's syndrome or disease, depending on whether it is due to hyperplasia or due to tumor formation.

This would make it appear that this is a common finding. It occurs whether you give small doses for a long time, or large doses for a long or short time. So far as I know, this could neither be prevented nor cured with any degree of con-

sistency, so this is a characteristic finding for the administration or the presence of excessive corticosteroids in the body.

Another of the common complications of corticosteroid therapy is the problem of activation and perforation of pre-existing peptic ulcer, and apparently an activation or the production of peptic ulcer which did not previously exist.

In contrast to osteoporosis, this is true only when corticosteroids and ACTH are administered, particularly in fairly large amounts for the treatment of the disease. Now, whether this is due to the rate at which we give it, or what, I don't know. This is in very sharp contrast to the fact that in Cushing's disease,

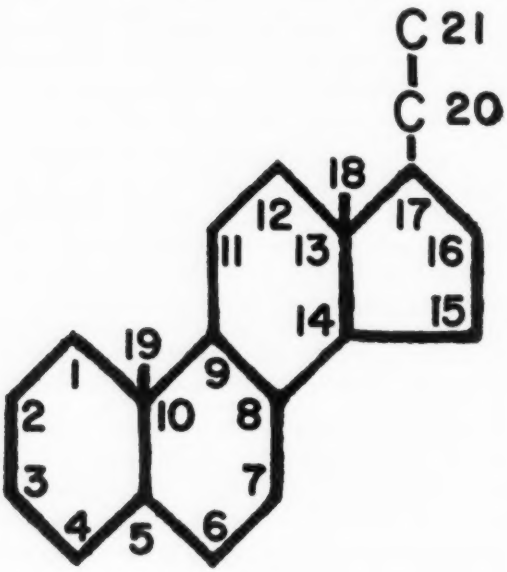


Fig. 1

which is, again, the disease of natural hypercorticism, peptic ulcer is probably rarer than seen in the general population.

A few of us who have been interested in this problem have been looking for cases of Cushing's disease with peptic ulcer. So far I myself have seen only one single individual with proven Cushing's disease and a concomitant peptic ulcer. I believe, therefore, that there is here a distinctive difference.

Now, it may be, as many people have said, that part and parcel of the collagen diseases or some other diseases which are being treated with corticosteroid is a basic predisposition to peptic ulcer. Whether this is true or not, I don't know. I know how to make the decision; however, I think that the part

that I should like to mention and which I hope will bring some controversy from the panel, if nothing else, is that there is a sharp distinction in this instance between the administered steroid and ACTH, and the effect on the gastrointestinal tract of endogenous corticoids being produced.

Dr. Kaplan:—Thank you, Dr. Segaloff.

Dr. Hyde, will you proceed with the chemistry of the steroids?

Dr. Paul M. Hyde:—You are probably wondering: why be interested in the chemistry of the steroids? It is a natural question. When I have finished, I hope you will have found the answer.

Today, more than ever before, we have many compounds on the market, steroids of known biological activity but made in the laboratory, or artificial. Unless one has knowledge of what these compounds look like, what they are, one will be unable to distinguish between compounds of better or less activity in retaining sodium or depositing glycogen in the liver.

These compounds are known as minerocorticoids, or glucocorticoids respectively. These I will take up in detail later.

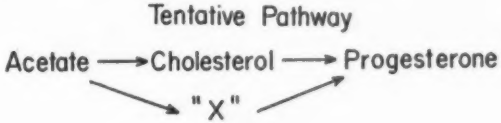


Fig. 2

You probably are all aware of this structure (Fig. 1). You have seen it many times. It is a basic numbering system in the steroids. It goes around four separate rings, A, B, C, D, and positions 1 through 17. No. 18 is the angular-methyl group. No. 19 is the same. You have seen 19, nortestosterone. It is testosterone without the methyl group at 19, and is like Nilevar in this respect only.

In the body, acetic acid or acetate is transformed into cholesterol and possibly another substance, labeled here as X, before it is transformed into the progesterone in the adrenal and other tissues (Fig. 2).

In the adrenal, progesterone can be converted to 17-hydroxy-progesterone. We just add a hydroxy group at position 17, the same position you know so well in 17-ketosteroids. If we have the correct enzymes in the adrenal, we will have the 21-deoxy-cortisone, or the 11-deoxy-cortisone formed. We just add hydroxyls at positions 11 and 21.

When the reverse takes place, that is a double hydroxylation, the compound, known as cortisol or hydrocortisone is formed. In the adrenogenital syndrome we have an enzymatic defect. The adrenal cannot hydroxylate at the

11 position or at the 21. We have less cortisone or hydrocortisone produced; other compounds build up and are metabolized and these give rise to properties we know so well as the adrenogenital syndrome.

We have three glucocorticoids (Fig. 3). Compound F or hydrocortisone is the major, and possibly there are more than 3 glucocorticoids secreted by the adrenal. In human adrenal venous blood we have been able to isolate hydrocortisone and corticosterone in significant quantities.

Cortisone, the third glucocorticoid, is found in very small quantities in experimental animals and rarely in humans, circulating as such. It differs from the hydrocortisone only in position 11, having a ketone instead of a hydroxyl

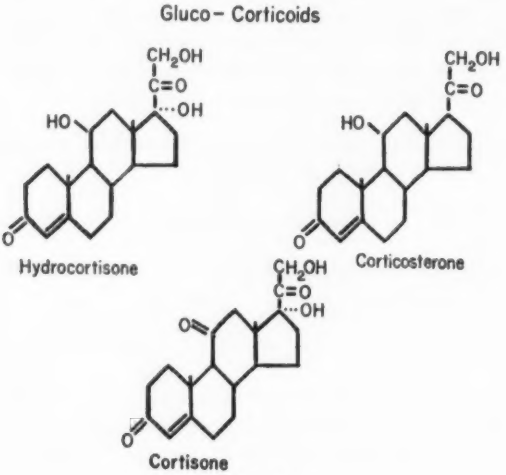


Fig. 3

group, yet its biological activity is a little less than hydrocortisone. Corticosterone is much less active as glucocorticoid than hydrocortisone.

Desoxycorticosterone has been given for a good many years for the control of salt, sodium, in the body. It is closely akin to aldosterone, recently isolated by three different laboratories. The structure of aldosterone is quite different in that we have another ring containing an oxygen off of the C ring. Position 18 has a carbon linked to an oxygen bonded at position 11 (Fig. 4).

You may wonder why I am going through a discussion of these details.

These are the compounds commercially available, known, I think, directly not as synthetic but as artificial steroids (Fig. 5). We have listed on the right their biological activity in the rat as far as the deposition of the liver glycogen is concerned[1].

Hydrocortisone is shown here, as the basic structure. The positions of substitution are shown, numbered both on the figure and in the table. The addition of a double delta bond between positions 1 and 2 on this compound, now called prednisolone increases biological activity four-fold. You can increase the activity still further by other substitutions. The 2-methyl increases it 10-fold, the 6 alpha fluoro 12 times. If you put a 19 alpha fluoro in, you can increase it 20-fold, in other words, one-twentieth the same weight of hydrocortisone gives the same biological effect on the rat. Sixteen-alpha-methyl hydrocortisone, related to one of the more recently discovered compounds, is 30 times as active in this phase.

If we compare on an experimental animal, the different biological activities of a single compound, glucocorticoid, and the minerocorticoids, measured by liver glycogen and sodium retention here, by putting in both delta-1 and 9-alpha fluorohydrocortisone, you have increased activity 30-fold (Fig. 6). If you

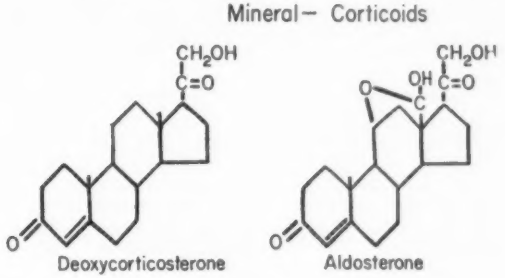


Fig. 4

put in two fluoro atoms at positions 6 and 9, you have increased the glycogenic activity 400-fold, but there are other problems that come in, as shown by the next one, the 2-methyl, 9-alpha fluorohydrocortisone. You have increased liver glycogen activity by a factor of 38-fold, but also the sodium retention is more than a naturally occurring aldosterone.

If you compare that with hydrocortisone, 0.04, with the aldosterone figure of 30, and the 2-methyl, 9-alpha fluoro compound with a factor of 80, the compounds do not necessarily have the same increase in the two perimeters of activity at these two different sites or many other sites.

Many of the commercially available compounds have different biological activities. The salt retention and the glucocorticoid activity may not go together.

In man we do not get as striking results as shown here with experimental animals, but it behooves us to be aware that we can have significant increases in sodium retention with just slight increases in glucocorticoid activity.

In the human, hydrocortisone is transferred by the tissues of the liver, kidney, and plasma itself into two other easily measured compounds (Fig. 7).

The one that is probably best known is tetrahydrocortisone. This is usually measured in urine, in the clinical laboratories, by the important Porter-Silbar test, or Reddy, Jenkins and Thorne procedures. We have a reduction of the biological activity associated with an A ring, with the destruction of the alpha-beta unsaturated Ketone. Changing the Ketone to an alcohol at position 3, we have tetrahydrocortisone. Tetrahydrocortisone is found in much smaller quantities.

If we give the same amount of steroids by three different routes of administration, we will get different blood concentrations. Here is an experiment[2], where 200 mg. of hydrocortisone was given to a 35-year old normal male medical student. Figure 8 shows the experiment done at the National Institutes of Health with isotopic compound F, in micrograms per hundred ml., and time in hours on the horizontal axis. After intravenous administration we get a gradual fall from approximately 150 mcg. to, at the end of three hours, around 80. If we give the material by mouth, we get a much higher value, 220, for the plasma hydrocortisone, at 90 min. than by intravenous route. If we give the

Hydrocortisone

		Rat Liver Glycogen
	Hydrocortisone	1
Δ'	Hydrocortisone	4
2 Me	Hydrocortisone	10
6 αF	Hydrocortisone	12
9 αF	Hydrocortisone	20
16 αMe	Hydrocortisone	30

Fig. 5

same quantity by intramuscular injection in two sites, we get a much lower value than by the other two routes; however, after nine hours we have the same quantities of hydrocortisone in the plasma, whether we give the material by mouth or by intramuscular injection. We have virtually no circulating hormone after intravenous injection at this ninth hour.

A clue as to the biological activity of the artificial steroids is seen in this illustration (Fig. 9)[3]. We have given 70 mg. of hydrocortisone intravenously to the same person on another day. Here we have 17-hydroxy-corticoids vs. time in hours over a six-hour period. The initial plasma values at one hour do not differ significantly. At the end of two hours the plasma values are very close, at four hours they are identical, but at six hours we have quite a difference. Almost twice as much of biological active material is present in the plasma after administration of the delta-1 prednisolone-type compound.

You may ask why. Prednisolone is excreted by the human in the urine almost unchanged. The liver is unable to attack the delta-1 compounds and break them down by normal detoxification or metabolic processes. It eliminates

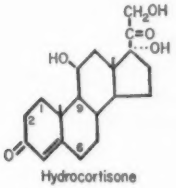
them quite fast into urine. After a single injection of the hydrocortisone, half of the material is completely eliminated by the body in four hours. It is a very fast-acting material.

Then the activity of these artificial compounds may be due to their prolonged stay in the plasma, resisting liver inactivation into less potent biological products.

Dr. Kaplan:—Thank you Dr. Hyde.

Dr. Skelton, will you tell us about the morphologic consequences of steroid administration?

Dr. Floyd R. Skelton:—As a morphologist I have placed myself in a rather unusual position since I do not have any slides. Much of what I want to review, however, will be more or less familiar to you, and slides would be of little assistance in illustrating my remarks. These will be confined to a description of those changes which occur in the gastrointestinal tract consequent to either interruption of the functional integrity of the anterior-pituitary-adrenocortical



Hydrocortisone

		Liver Glycogen	Sodium Retention
	Hydrocortisone	1	0.04
Δ',9αF	Hydrocortisone	30	30
6α,9αdiF	Hydrocortisone	400	
2Me,9αF	Hydrocortisone	38	80
	Aldosterone	03	30

Fig. 6

axis or to excessive exogenous administration or endogenous overproduction of adrenal steroid hormones.

When the literature on this subject is perused it is found that very little really is known. I think you are all familiar with the fact that in the Addisonian patient there is generalized atrophy of the mucosa of the intestine and stomach, the latter accompanied by a reduction in volume, acidity and enzymatic activity of gastric secretion. In order to study the temporal relationships between these changes and the onset of adrenal cortical insufficiency it has been necessary to revert to laboratory experimentation using the white rat[4]. The rat stomach, as you know, is made up of two parts, the fore-stomach which is lined by squamous epithelium and the pyloric region which is lined by true gastric mucosa. In the rat, as in man, adrenalectomy is followed by progressive atrophy of this gastric mucosa.

Characteristically the atrophy is apparent in the reduction in size of the individual cells that line the mucosal glands and in the decreased amount of mucus contained within the mucus-secreting cells that line the neck region of the glands. Consequently, the amount of mucus on the surface of the gastric

mucosa and in the gastric pit is reduced. Perhaps of greater importance than the reduction in mucus secretion is the reduction in number and size of the chief or zymogenic cells of the mucosa which have to do with the secretion of gastric pepsin. Histologically there is also a decrease in the number of zymogenic granules, the precursors of pepsinogen, and the ribonucleic acid contained in the cytoplasm of the remaining cells.

The above morphologic changes are reflected in the gastric secretory function of these animals, for there is a decreased volume of secretion, accompanied by a reduced acidity and pepsin content of the gastric juice, although the former is much less reduced in amount than the latter.

Steroid administration in doses calculated to approximate normal adrenal cortical secretion reverses these changes, although not entirely to normal. This

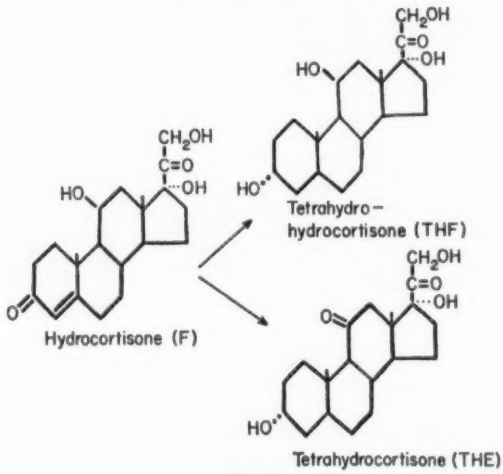


Fig. 7

is a rather nonspecific effect of the corticoids, because many of them will show the same change: indeed the simple restitution of electrolyte balance by giving sodium chloride shows some normalizing effect on gastric secretion.

Hypophysectomy, which removes the source of endogenous ACTH thus leading to adrenal atrophy and profound reduction in cortical secretion, although aldosterone secretion and electrolyte metabolism may be little altered, produces a greater effect on the gastric mucosa than does adrenalectomy. This may well be due to the loss of other trophic hormones besides ACTH. This speculation has received support from observations in experimental animals showing that the administration of growth hormone and thyrotrophic hormone tend to prevent the atrophy and reduced secretory activity of the gastric mucosa

in hypophysectomized animals. This is further normalized by the administration of ACTH. Furthermore, combined adrenalectomy, thyroidectomy and gonadectomy in the same animal produces cytological and functional changes in the gastric chief cells which are comparable to hypophysectomy thus showing that, while the adrenal cortex may be the most important endocrine gland affecting the gastric mucosa, other endocrine organs also exert some effect.

The changes in the mucosa of the duodenum and small intestine after adrenalectomy or hypophysectomy are much less well known. In so far as morphology is concerned the goblet cells are reduced in number, and their mucus content as well as the amount on the mucosal surface is also reduced. Administration of corticoids to the adrenalectomized animal, or ACTH to the hypophysectomized animal returns the mucus content of these cells to normal and sometimes to above normal levels.

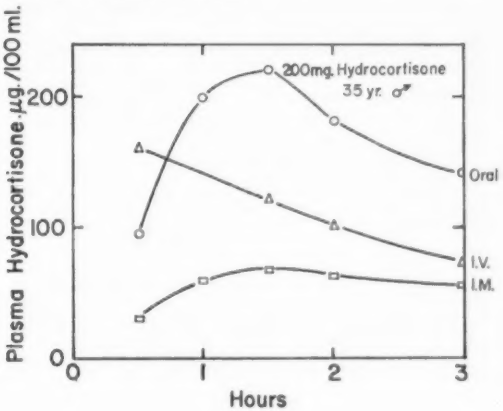


Fig. 8

This brings us to a consideration of the relationship between stress, pituitary-adrenal activity and the production of gastric ulceration. We know that in response to stress the pituitary-adrenal axis is activated with a resultant increase in the secretion of glucocorticoids. It has been shown by Gray and his associates[5] that under these circumstances there is an increased secretion of acid and pepsin by the gastric mucosa. Simultaneously there is a secretion of pepsinogen directly into the blood which transports it to the kidney where it is transformed into uropepsin and excreted in the urine. Any increased gastric pepsin secretion is therefore reflected in a rise in urinary uropepsin. It has been demonstrated in both dog and man that administration of corticoids or ACTH leads to increased gastric pepsin secretion and elevated urine levels of uropepsin. These findings which simulate the conditions existing in at least some cases of active peptic ulcers and the common association between stress and the induction of peptic ulceration have led these investigators to postulate active adrenal

cortical participation in the genesis of this disease. Furthermore this mechanism is suggested as the manner through which exogenously administered corticoids produce such iatrogenic peptic ulcers.

Not all investigators or clinicians are agreed that the mechanism proposed by Gray is the key to adrenal cortical participation in the pathogenesis of peptic ulceration. Nevertheless, the abundant evidence cited earlier shows that the adrenal cortex does exert a profound influence on the gastrointestinal tract and it behooves us as physicians and scientists to continue to search for the link between stress, the adrenal cortex and gastric ulceration—for the weight of evidence today certainly suggests that such exists.

Dr. Kaplan:—Thank you, Floyd.

I was reminded some few years ago that there is a difference between clinicians and scientists. Scientists reveal facts; clinicians report observations.

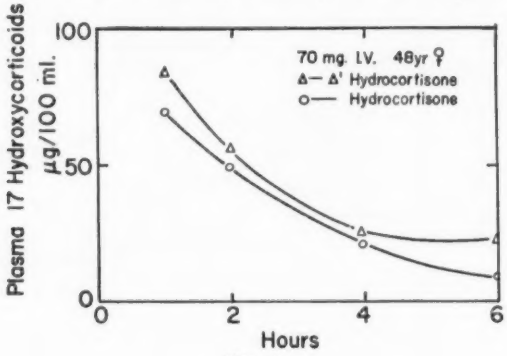


Fig. 9

Now, the clinical aspects of the steroids in gastroenterology will be approached. I have assumed the responsibility of discussing some of the medical viewpoints of therapy as well as the complications. Dr. Boyce will follow with the surgical aspects.

(Slide) This drawing by Netter illustrates the hormonal and neurogenic pathways of rage. It is symbolic of the reaction of the body to any stressor. Just as in the production of disease, the hormonal system plays a part, so in the treatment, we must consider its role. The pituitary adrenal axis is thought to be involved in all diseases. It is not the sole reaction, nor necessarily the main one, but that there is a disturbance in steroid metabolism is fairly well accepted. On this basis, we feel justified in discussing steroid therapy in diseases of the gastrointestinal tract.

May I say that there is only one absolute indication for steroid therapy—that is adrenal insufficiency. This has been brought out in many clinical discus-

sions at various times. We look upon steroids, however, as a valuable adjunct type of therapy. Our principal interest and development has centered about the use of steroids in short-term treatment.

It is not only our purpose this morning to review, but also to give a few highlights, possibly to recall and refresh your minds on a few of the accepted as well as the controversial applications of steroids in gastroenterology.

One of the most common lesions in the mouth, on the buccal mucous membrane, is the apthous ulcer. In 1955 Erich made the profound statement in his celebrated textbook that there is no known cause for apthous ulcer, and there is no treatment of value. The double-blind controlled study of 120 patients of Sircus in 1957 reinforced this.

Inasmuch, however, as the antiinflammatory action of the glucocorticoids has been touched on by physicians in all phases of various diseases, it occurred to Truelove of England, among others, to apply this principle to the oral mucous membrane. Ointments had been unsuccessful in the hands of Fisher, Riven and Barton, but Truelove reported highly favorable results in 52 patients using lozenges of hydrocortisone hemisuccinate.

The treatment is simple and safe. A tablet is placed against the ulcer, or ulcers, and allowed to dissolve slowly. This is prescribed on a q.i.d. basis until healing takes place. Supplemental antibiotics are discouraged. Pain is relieved promptly.

My personal experience has been limited, but the tablet apparently affords considerable relief from pain. I am not yet in a position to claim that healing is faster or recurrence less frequent. It is another medication to add to your armamentarium for these resistant, recurrent, irritating, and exasperating oral lesions.

Esophageal lesions occurring as part of a systemic disease, such as scleroderma, have been reported as receiving some benefit, but this is not universally accepted.

Esophagitis is supposed to be one of the complications of steroid therapy. Still one group of conservative investigators reported 9 of a series of 12 improved on corticosteroid treatment.

Lye burns of the esophagus when treated promptly with steroids and antibiotics have healed without stricture or other complication.

Acute hemorrhagic gastritis was controlled with steroids in individual cases reported by Deutch et al, and by Meredith and Rector. Both patients had been submitted to subtotal gastrectomy, and repeated explorations for recurrent massive gastrointestinal bleeding. Meredith and Rector based their resorting to cortisone therapy on its "known anti-inflammatory effect and its success in the treatment of hemorrhage in ulcerative colitis". The treatment is obviously di-

rected at controlling capillary fragility and blood coagulability. The many factors involved preclude any lengthy discussion at this time.

It is conceivable that steroids might replace subtotal gastrectomy in those instances of gastroduodenal bleeding in which generalized oozing or diapedes is recognized at the operating table–there being a failure to demonstrate a localized area of bleeding.

This brings to mind a true story of two of our eminent surgeons who were in surgery the same afternoon with cases of massive upper gastrointestinal hemorrhage. One performed a subtotal gastrectomy–the other merely explored, opened the stomach and duodenum and finding no single area of bleeding–got out. It is well over 10 years now, and annually these men compare notes. Neither patient has had a recurrence of bleeding.

I think it will be a long time before we will employ steroids except as a last resort measure in acute hemorrhagic gastritis. Yet, I don't think anyone of us would hesitate to use it as an adjunct in a known case of gastrointestinal bleeding in purpura.

Dubois noted the healing of a known peptic ulcer in a case of *lupus erythematosus* while on treatment with triamcinolone.

There are a few reports in the literature on the treatment of peptic ulcer with cortisone. This has yet to become an adjunct in the usual therapy of the usual ulcer. ACTH, on the other hand, has been condemned.

Steroids have been recognized to be of value in regional ileitis, sprue, and Whipple's disease. In the former, the antiphlogistic action aids in the control, but does not cure. In the malabsorption syndrome of sprue, steroid therapy is based on the experimental evidence of the role of the adrenal cortex in regulating the rate of glucose and fatty acid absorption from the intestinal tract.

Whipple's disease is thought to belong to the collagen family. The effectiveness of steroids in *periarteritis nodosa, lupus erythematosus* and scleroderma as systemic diseases has been well documented. Theories have been offered, but as yet there is no evidence of any basic adrenocortical deficiency.

In the hands of men like Kirsner of Chicago and Zetzel of Boston, the routine use of steroids in acute ulcerative colitis may prove most effective. It is still felt in most quarters, however, that only in the acutely ill, fulminating type on the one hand, and in the chronically ill who had failed to respond to the usual therapy or in the preoperative preparation for colectomy should their use be encouraged. ACTH seems to be preferred over the parenterally given cortisone.

Topical steroid therapy in the form of rectal drip using hydrocortisone hemisuccinate has been advocated by Truelove of England and by a group in

Texas. It appears that benefit might be anticipated in diseases of the rectum and possibly lower sigmoid, but the relapse rate appears high.

There is no new evidence to justify the use of steroids in uncomplicated cases of acute viral hepatitis. They are still advocated in the fulminating, progressively deteriorating as well as in the chronic intractable cases.

Mention has been made that ACTH might be useful in differentiating between cholangiolitic hepatitis and extrahepatic jaundice. Forty units of Acthar jel every 12 hours for 4 days revealed a drop of more than 50 per cent in the serum bilirubin in the latter as compared with 65 per cent decrease with hepatitis. These figures, however, are too close to be of definite diagnostic value.

Acquired hemolytic anemia in association with viral hepatitis is thought to be due to either a decrease in the resistance of the RBC's to hemolysis, abnormal destruction of the RBC's by a sensitized organ like the spleen, a hemolyin or hematoxic substance of endogenous origin due to liver impairment. Steroids are of definite value regardless of the cause.

Cortisone is administered to cirrhotics with a known hazard. The presence of esophageal varices offers a great handicap. Corticosteroid therapy in cirrhosis of the liver has few enthusiasts except those of us who are willing to use any therapy in a last ditch fight.

Certainly in hepatic coma, our backs are against the wall. A recent report by Persac and Hessing described spectacular response to massive doses of cortisone. Using 1,000 mg. of cortisone in daily dosages, their patients became alert, rational, and able to eat. Their patients eventually succumbed to either massive gastrointestinal hemorrhage or liver toxicity, but these responses are worthy of being called to your attention.

Symptoms of postcholectomy syndrome without demonstrable pathology is a source of great discomfort not alone to the patient, but to the gastroenterologist. In the woman, menopausal or postmenopausal, who has failed to yield to the regular pharmacopia, with no response to estrogens, androgens, individually or collectively, the use of small daily doses of cortisone have proven surprisingly successful. Don't ask why.

The use of steroids in malignant types of acute hemorrhagic pancreatitis has not been accepted in many places outside of New Orleans. We have advocated its use based on a series of observations, but admittedly are lacking both in controlled studies as well as proof by animal experimentation. Among the enthusiasts are Cook and Rogers of England, and Fritch of Austria.

Much has been written condemning steroids in pancreatitis. There are reports of acute pancreatitis in children developing during steroid treatment for asthma and polymyositis. The Yale group reveal that in controlled autopsy studies there was a notable increase in the number of focal pancreatities in those on

steroids. Janowitz and his group found a diminution in the external pancreatic secretion after steroids were administered. This, they hypothetically conjecture, causes stagnation and damage of the acinar tissue.

Animal experimentation has brought forth the work of those who were able to produce areas of pancreatitis in rabbits by the administration of steroids. Hans Selye produced pancreatic lesions in rats with Stylomycin. This was aggravated by Cortisol. It has been called to my attention that at a recent meeting of the American College of Surgeons, Zollinger reported acute pancreatitis produced in dogs by incubating pancreatic enzymes with bile and injecting it into the pancreatic duct. Only 48 per cent of those receiving cortisone lived—100 per cent of the controls survived.

It is obvious that the bulk of evidence is against its use. Yet, as a clinician, the spectacular, life-saving observations made and recorded by many of my colleagues as well as myself have been impressive. We have come to look upon acute hemorrhagic pancreatitis as an inflammatory process which may well be due to an antibody reaction, much the same as that described by Witebsky on thyroiditis and Dameshek on collagen diseases. In other diseases of hypersensitivity, steroids have been found to be very useful, but never 100 per cent. Our clinical successes have motivated us to attempt to produce this disease experimentally. There is no report at this time.

I am convinced that the prolonged use of steroids in chronic relapsing pancreatitis is unwarranted. In acute exacerbations, as in acute hemorrhagic pancreatitis, these adrenal cortical hormones are of definite value.

Dr. Boyce, will you have something to say about the surgical aspects?

Dr. Frederick Fitzherbert Boyce:—It is apparent that very little is left for me to say with regard to the therapeutic use of steroids in surgical diseases. I will say, however, that it is well documented that the use of steroids can produce dramatic remissions in certain diseases which may require surgery. I will touch briefly on the surgical aspects of some of the diseases which have been mentioned.

Probably I will begin by using acute hemorrhagic pancreatitis as my first illustration.

It is well known that mortality of acute pancreatitis varies in reported literature from some 12 per cent by Becker, to some 33 per cent by Paxton and Payne, but this is very easily explained. In the series reported by Becker, 84 per cent of the cases were of the subacute edematous variety, whereas in the series reported by Paxton and Payne the hemorrhagic necrotizing variety predominated. The mortality of acute pancreatitis is overwhelmingly in the hemorrhagic variety. Under the circumstances, any drug which would reduce in any way the morbidity and mortality of acute hemorrhagic pancreatitis should be used even if it is associated with danger.

We do not know how the steroids act in acute pancreatitis. Some believe that using them buys time, thereby giving our usual standard method of therapy a better chance to be effective. Steroids increase hydrochloric acid secretion in the stomach, which in turn is associated with an increase in the production of secretin. Secretin activates pancreatic activity. This, however, can be controlled or overcome by constant gastric suction.

The use of steroids in regional enteritis is a very interesting one. I have advocated their use under certain conditions, namely:

1. When the patient refuses surgery; 2. when the patient is unfit for surgery at the time; 3. for patients in whom surgery is impractical because of the extensiveness of their disease—removal of the greater part of the small and large bowel would leave them intestinal cripples. The desirable effect of steroid therapy lies in relieving systemic manifestations, such as fever, toxemia, stimulating appetite and gaining time for spontaneous remissions.

The remarkable improvement which may occur when steroids are given in conjunction with other well established forms of treatment to a patient with ulcerative colitis may eliminate or postpone the need for surgery. By the same token, if operation is necessary, the improved preoperative status of the patient frequently allows the surgeon to complete the operation (ileostomy and colectomy) in one stage rather than in multiple procedures.

Recent reports in the literature indicate the value of ACTH and cortisone in the treatment of recurrent massive gastric bleeding after subtotal gastrectomy which is due to capillary fragility associated with erosion of the gastric mucous membrane. This local capillary fragility may be converted to capillary resistance by corticosteroids.

Statistically the steroids cannot be incriminated entirely for the reactivation and perforation of peptic ulcers. Finally, I would not like to leave the impression that steroids produce only a rosy picture in ulcerative colitis.

Recently, a decided adverse effect has been recorded in the literature. Occasionally steroids have produced disintegration of the bowel wall, making surgery imminent with its associated increase in morbidity and mortality.

Dr. Kaplan:—Thank you, Dr. Boyce.

We will now get down to the "meat" of the situation. I am sure there are many questions on this controversial subject. We are not experts in the field. If anyone disagrees with what we have to say, I will hold the floor open to him to stand and give his opinion.

We have a few questions here, and I will pass them along. Dr. Segaloff, will you answer one?

Dr. Segaloff:—May I start off by making a general comment?

As some of you know, I am a purist about a lot of things and one of the things that makes my few remaining hairs stand straight up is to find that the title of this panel discussion is a "Panel Discussion on Steroids in Gastroenterology," and to hear everybody talk about steroids. Now, I have been working with steroids for more years than I care to count, and the steroid I usually have used in the gastrointestinal tract is a bile acid. There are all sorts of steroids, even though I am sure what everybody means is corticosteroids. The fact still remains that they are only one type of hormonally active steroids.

Other steroids that were mentioned today and that I see mentioned elsewhere in the program have nothing at all to do with cortical hormone activity. I think that particularly now, as Dr. Hyde pointed out, we are getting further and further away from natural corticosteroids and getting out to steroids that are not only corticosteroids but also have very specific types of activity. It would help, when thinking as well as referring to them, to be more specific.

Dr. Kaplan:—I think your criticism is justified, Dr. Segaloff, and I apologize. I think that this term has, unfortunately, been accepted in most of the clinical circles. So we adopted the title. In one of the publications they talk about sterotherapy. It is a newly coined word. You have seen it. If you will accept our apology, we will go on from there.

I passed a question or two on to you. Would you mind starting the questions?

Dr. Segaloff:—The question here is: "Do you feel that the administration of ACTH periodically while a patient is on long-term oral steroids, aids in preventing adrenal atrophy?"

The question, I gather, has wider implications. Actually giving ACTH is enough aid. If you give it frequently enough, at frequent enough intervals, you prevent adrenal atrophy, but the question, I believe, is whether this is dangerous or not.

I don't know what the answer to this is. Actually after long-term therapy, it is probably the failure to secrete ACTH that gets you into difficulty, rather than adrenal atrophy.

It is my own preference to use ACTH therapy at the end of steroid therapy rather than intermittently during steroid therapy, and the reason I say this is not that it gives evidence of being better, but it is easier.

Dr. Kaplan:—Dr. Hyde, what is the effect of glucocorticoids on the level of blood sugar, and what is the mechanism of action?

Dr. Hyde:—Glucocorticoids, given in physiological amounts, will affect the level of blood sugar very little. The primary effect is in the liver, to increase glycogen deposition from glucose. You may get a slight decrease in blood sugar, but it is only momentary until the other hemostatic mechanisms take over and you get more glucose put in the blood.

Dr. Kaplan:—Dr. Hyde, there is a question as to whether you have clinically observed diabetes following prolonged therapy. How do you account for that?

Dr. Hyde:—Steroid diabetes, as you know, is caused by increased amounts of glucocorticoids.

These compounds, when used in excess, produce greater than normal amounts of glycogen, being formed from amino acids. The glycogen is transformed into glucose at increased rates and put into the blood stream. Some authors say that the significant glycosuria may result from a reduced renal threshold for glucose. The precise cause of the insulin resistants in this syndrome has not been elucidated.

Dr. Kaplan:—I don't know whether that answers your question. If not, is there anyone else who wishes to answer or comment about this question?

To get the clinical side, Dr. Boyce, do you have a question?

Dr. Boyce:—"Outline treatment of gastrointestinal tract perforation complicating long-term steroid therapy." Certainly in any perforation of the gastrointestinal tract surgery would have to be considered. Closure of a perforated peptic ulcer with or without gastrectomy, depending upon the patient's condition and duration of the perforation, would have to be done. Perforations of the colon are probably best treated by exteriorization and decompressive colostomy.

Dr. Kaplan:—Dr. Boyce, would you comment on the use of steroids at the time of surgery?

Dr. Boyce:—In the period immediately preceding and following the surgical procedure the patient would have to be covered by adequate dosages of steroids.

Dr. Kaplan:—It is very interesting to read a recent publication by Kirsner and Goldfarber of Chicago answering the question relative to the incidence of perforation following ACTH therapy. In their series they did not find an increase after ACTH. They had specimens examined microscopically and came to the conclusion that there was not sufficient evidence to justify the prevailing impression that ACTH therapy was responsible for the increased incidence of perforation.

We might comment a minute on the question of gastrointestinal hemorrhage complicating long-term steroid therapy. There is surprisingly little in the literature on the position one assumes in regard to steroids once the hemorrhage is manifest. I am told that Dr. Dameshek feels that the whole adrenal extract should be given in order to combat hypoadrenalism. In our few cases it has proven very satisfactory.

Gastrointestinal hemorrhage is a dreaded complication of steroid therapy. The shock from the loss of blood is in itself sufficient to concern us. Add to that, the effect of steroid withdrawal; it is no small wonder that mortality is high.

Five c.c. of whole adrenal extract may prove beneficial in preventing an adrenal crisis. Our cases have survived either because of, or in spite of its administration.

Do you have any comment on that, Dr. Boyce?

Dr. Boyce:—In the first place it would depend upon the rate of bleeding. In the face of massive bleeding from erosion of an artery, for example, duodenal ulcer eroding the gastroduodenal artery, surgery is indicated after preparation of patient. On the other hand, if the bleeding is less massive and the patient can be stabilized by the administration of one pint of blood every eight hours or longer, the patient could be treated conservatively.

Dr. Kaplan:—We are interested primarily in the use or disuse of steroid therapy.

I have another question here: "If peptic ulcer develops during steroid therapy, would you continue to discontinue steroid therapy?"

Most of the profession are using antacids and anticholinergics in prolonged steroid therapy. The action one takes depends in a great measure on what primary disease he is treating. A seriously ill patient with *L.E.* or *periateritis nodosa* who was responding to steroids, would of necessity continue treatment. An asthmatic, in remission, being maintained prophylactically, might be better off discontinuing the hormone.

Dr. Skelton, do you have a question?

Dr. Skelton:—I have one question here: "Can you morphologically distinguish a gastric ulcer co-existent with rheumatoid disease from one caused by the administration of steroids?"

No, I can't tell any difference nor do I know how one could. We have a good deal to learn yet about how the steroids produce gastric ulceration despite our present understanding of some of the ways in which these hormones affect the gastrointestinal tract. It may be that adrenal steroids do not produce ulceration directly but rather, by their presence in adequate amounts, permit other factors to work more effectively on the mucosa thus leading to ulceration. In this way they would act as "permissive" rather than "causative" agents.

Dr. Kaplan:—Dr. Segaloff do you have an unanswerable question?

Dr. Segaloff:—I have a series of questions which I think would require really a Solomon to answer. The first question, I think, is unanswerable, at least in part: "Would you ever use the steroids without simultaneous antibiotic coverage, and what is your experience with the rise in resistant staph infections where there is such a simultaneous usage?"

Now, actually our experience in seeing patients—and I suppose we should point out that we usually see the people that other people get into difficulty—is that the spectrum of infections that can be lit up by giving steroid therapy in large amounts is so wide that I don't know of any antibiotic or group of anti-

biotics which you could give that would really prevent them. For example, one of the complications that we have seen is the pulmonary spread of nocardiosis, which one could not treat successfully, so far as I know, with any of the available antibiotics, but which responds very well to sulfadiazine.

We have also seen, as many of you have, the spread of acid-fast infection as well as staph and other types of infection. It would be nice if we had a broad-spectrum antibiotic that would handle all of these infections. If we did, I think we ought to give it along with the corticotherapy, but, since we don't have it, I think we have to be cautious and watch our patients, and there isn't any substitute for that.

The next question, which, again, I think, is either difficult or impossible to answer: "What is the safe period of time in which to gradually decrease and end steroid therapy after prolonged usage, such as two or three years?"

The answer is that there is no such thing as a safe time in which to do this. Many patients who have been on steroid therapy either of oral or parenteral type, can never be weaned from corticosteroid support no matter how gradually you reduce the dosage. Some of them, whether the dosage is reduced gradually or abruptly, will have a rebound and take over their own steroid production for ordinary life, but when faced with some stressful situation, will be unable to respond to it. All you can do in their situation is to reduce the dosage gradually and watch for the onset of adrenal insufficiency, which I hope you can all recognize.

Then the third one, to which I don't know the answer, and I gather the others don't either, is: "Are steroids useful in functional hypoglycemia?"

My answer to this would be no, though I don't really know whether this is the right one.

Dr. Kaplan:—I think Dr. Creek has observed a great number of cases of hypoglycemia. If I remember correctly, he felt that steroids helped these patients. How and why, I am not prepared to say right now. To be sure, it has something to do with glucose metabolism.

Next question: "When using ACTH in ulcerative colitis, do you use an antibiotic at the same time?"

Yes, I would think so. We do not alter our routine therapy in any disease when we use steroids. I certainly would advocate their continued use in ulcerative colitis. I would be afraid to give it up in almost any disease where infection might play a part.

There is another question here: "What is the effect of steroid therapy on the fetus, that is, in the ulcerative colitis of pregnancy, or with pregnancy?"

I don't know. I would feel that certainly the ulcerative colitis of pregnancy ought to be handled.

Would you want to answer that, Dr. Segaloff?

Dr. Segaloff:—Actually this is a very interesting question. We have tried to find whether or not there is any evidence in man of the production of the type of abnormalities that the corticosteroids produce in experimental animals. The problem is that for practical purposes you would have to be treating the patient when she became pregnant, and it turns out that most of the patients that had been treated and reported in the literature were started after the first trimester.

We have been able to run down here in town only two instances of people treated straight through the pregnancy with fair doses of corticosteroids, and both of them delivered perfectly normal children, so, for what this is worth, this is what we have been able to find out.

It may be that Dr. Skelton can tell us more of the finding of abnormality than we have found. We haven't found any. One man is starting with cleft palates and working backwards to see if he can find any connection with those who have had excessive steroid therapy.

Dr. Skelton:—I don't think there is any evidence in the human being that steroid therapy adversely affects the developing fetus. In certain experimental animals steroids can induce congenital abnormalities, but these observations have not been transferred to man.

Dr. Kaplan:—Dr. Skelton, do you have another question?

Dr. Skelton:—This question is: "Will a low cholesterol diet such as now advocated in the prevention of atherosclerosis (ageing process) adversely affect the adrenal corticosteroid response?"

I do not think so. The cholesterol that the adrenal uses to make corticosteroids comes from acetate; hence it is independent of the amount of cholesterol in the diet.

One other short question: "Would a dose of 2 to 4 mg. of prednisolone given for several months be sufficient to cause permanent damage to the adrenals?"

Well, the dose is reasonably small, but it may indeed have some effect on the adrenal when given for a prolonged period. I don't believe, however, that any permanent damage would result. In experimental animals hypophysectomized for many months the atrophic adrenals can be brought back to a normal appearance by the administration of ACTH. The human being, even when steroid-induced adrenal atrophy is profound and of long-standing can do likewise, although it may take some time to accomplish this.

Dr. Kaplan:—Dr. Segaloff, do you have anything to say about that?

Dr. Segaloff:—No.

Dr. Boyce:—I have a question on the use of corticosteroids in postoperative shock conditions exclusive of hemorrhagic shock. If you are not dealing with

electrolyte imbalance, myocardial dysfunction or embolism in the immediate postoperative period, probably the corticosteroids are helpful in combating this type of shock.

I have a second question: "Would you consider colectomy in a case of ulcerative colitis where the nutrition is good but structural bowel changes appear relatively unimproved and bowel movements are watery and frequent, but apparently not too distressful?"

I would take it for granted that this patient has been on steroids and has had no improvement. If, however, the nutrition is good and the patient is not distressed too much by frequent bowel movements, I would hesitate to do a colectomy; on the other hand, if nutritional change is not good and the diarrhea was distressful, I would not hesitate to do colectomy.

Dr. Kaplan:—I know it is past the hour. Do you want to hear the rest of the questions, or would you like to call it to an end? There are one or two left here.

One is on the mechanism of corticosteroids in control of bleeding in severe jaundice of hepatic degeneration and in marginal ulcer.

I don't know whether I can answer that. I can say that we found fibrinolysin to be present in several cases of cirrhosis, who were bleeding. We gave steroids and found their blood remained clotted a little longer. That may be a factor in the bleeding in hepatic degeneration. In marginal ulcer we may have a different problem, namely, capillary fragility. Does anybody know?

Dr. Boyce:—If the bleeding in marginal ulcer is the result of an arterial wall erosion, steroids will be of no value. If, however, bleeding is the result of increased capillary fragility and mucosal erosion, steroids would be of value by increasing capillary resistance.

In addition to its choleretic effect, corticosteroids may facilitate bile flow by diminishing inflammation and edema around the smaller bile canaliculi in the diseased liver. The decrease in the bilirubin level would be associated with improvement in the bleeding tendency.

Dr. Kaplan:—I am very grateful to the panel for their participation, and thank you gentlemen for your kind attention.

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THE MECHANISM OF BROMSULFALEIN EXCRETION*

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In 1924 Edwin C. White, working in the laboratories of Hynson, Wescott, and Dunning, prepared a disulfonate derivative of phenoltetrabromphthalein[1]. This substance called bromsulfalein (BSP) has become universally used as a measure of liver function and with the modification of Mateer et al[2] it is generally accepted as the most sensitive indicator of hepatic damage in the non-jaundiced patient.

There is considerable knowledge regarding the distribution and rate of excretion of BSP from the body. When injected intravenously in a normal subject, BSP is removed from the blood at a constant disappearance rate[3] until low concentrations are reached (below .2 mg. per cent). After the usual test dose of 5 mg. per kilo, normals show a blood concentration at 45 minutes of .4 mg. per cent (4 per cent retention) or below. Following intravenous injection BSP appears within minutes in high concentration in the bile. Excretion continues until after blood concentrations are nil. Using S^{35} labeled BSP in dogs, Brauer, Pessotti and Krebs[4] estimated that 80 per cent of the total dye removed from the circulation could be accounted for on the basis of hepatic extraction. Variable amounts of the dye are excreted by the kidneys and concentrations can also be detected within the gastrointestinal tract, fat, and muscle. Dogs poisoned with carbon tetrachloride and given a test dose of BSP show an increase in the extrahepatic storage of the dye accompanied by an increase in blood levels and renal output. It is probable, that in the human cirrhotic, a similar distribution occurs.

In decompensated cirrhosis, ready transfer of BSP in and out of the ascitic compartment does not take place and this fact should be taken into consideration in evaluation of the liver function test[5].

Contrasting to the data on the dynamics of BSP, relatively little is known of the mechanism of transfer of the dye from the blood to the bile. Possibly this is because workers have assumed that since BSP excreted in bile still retains its quality as an indicator, modification of its molecular structure has not occurred. There is, however, evidence that BSP is altered in the process of its excretion. Krebs and Brauer[6] describe chromatographic changes in BSP obtained

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from rat bile. These workers have found 2 fractions chromatographically distinct from crystalline BSP and compared the bile-type BSP of various animals. Brauer et al[4] using S^{35} labeled BSP in dogs reported evidence of "the occurrence of chemical changes in the molecule of the dye associated with the process of excretion in the bile." In another report[7] they mention that by the chromatographic analysis of dog bile, BSP can be recovered in 4 fractions, different from BSP and none of them colorless.

Various other attempts have been made to define the mechanism of BSP excretion. Cantarow and workers[8] using duodenal fistula dogs reported that at elevated serum bilirubin concentrations, bilirubin and BSP compete for a common excretory mechanism—the BSP being excreted preferentially. Cohen, Althausen and Giansiracuisa[9] studied BSP excretion in the human by challeng-

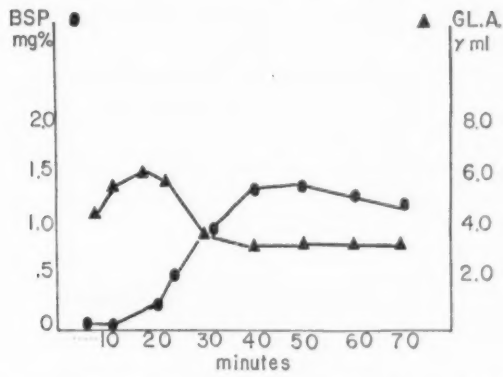

Fig. 1—The biliary concentrations of BSP and glucuronic acid following I.V. injection of BSP.

ing the hepatic excretory mechanism with different dyes. These workers concluded that BSP had a greater affinity than Rose Bengal for the transfer mechanisms involved in biliary excretion. Probenecid has been noted to have an inhibitory effect on the renal and hepatic excretion of BSP and Blondheim postulated[10] that the mechanism may be the interference with the conjugation of glycine. Simultaneous overloading with BSP and galactose produce no variation in these tests and it has been suggested[11] that separate mechanisms of metabolism exist.

Materials and Methods

To seek a clue as to the transfer mechanism involved in the hepatic excretion of BSP, comparative studies were made of the pure compound and the BSP found in the bile. All the tests were made on 7 human subjects with a draining T-tube in place. At least 48 hours were allowed for recovery prior to

study. Timed samples of the T-tube bile were taken for analysis following the intravenous injection of the usual dose of BSP (5 mg./kilo).

Bile specimens were checked for glucuronide content according to the method of Fishman and Green[12]. Glucuronic acid was determined in control bile samples and in timed specimens for 70 minutes following the intravenous injection of BSP. A second determination of glucuronic acid was then made following hydrolysis of the samples with 3/N hydrochloric acid (6 hours at 100

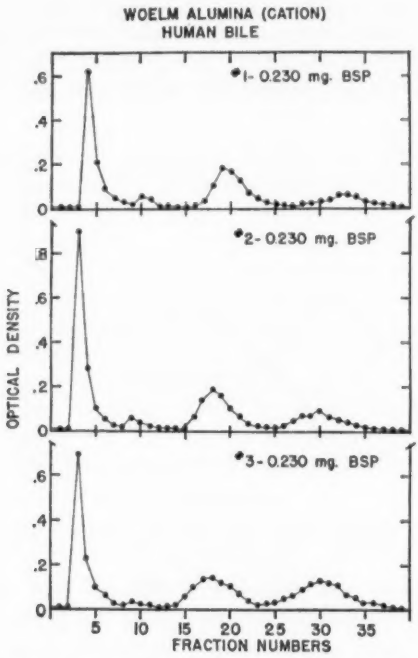

Fig. 2—Chromatographic plot of BSP excreted into the bile. Four fractions are shown (elution peaks 1 to 4 from left to right). Elution peak number 1 is similar to pure BSP.

degrees C.). The bilirubin levels of the samples were determined by the technic of Evelyn and Malloy[13]. BSP concentrations were measured by the method of Gaebler[14] utilizing blanks of the material to be analyzed.

Ascending paper chromatography before and after acid hydrolysis was done on similar bile samples. Whatman # 1 paper was used with acetone; propionic acid; water (75:25:30) as a moving phase. For two dimensional chromatographs a solvent of phenol:water (80:20) was used at right angles. A .1 per cent

ninhydrin in acetone solution was sprayed on chromatograms for the identification of amino acids and related compounds.

Column chromatography with cationotrophic alumina was performed on bile samples using a modification of the method of Krebs and Brauer[6].

Results

From a typical case in Figure 1 is plotted the biliary concentrations of BSP against those of glucuronic acid. These values for glucuronic acid reflect splitting of biliary glucuronides produced by acid hydrolysis of the samples. There is no demonstrable relation between the concentrations of BSP and glucuronic acid. The drop in the glucuronic acid level following BSP appearance in the bile is thought to be a dilution effect as bile flow increases. The bilirubin levels

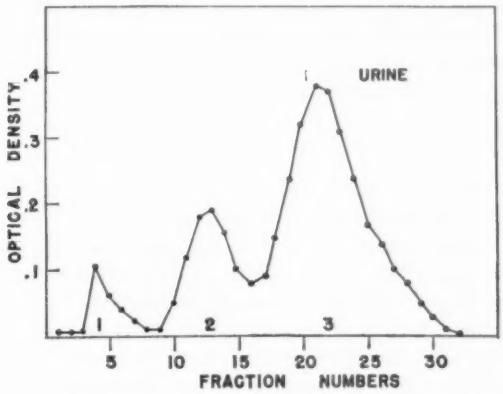

Fig. 3—The chromatographic plot of BSP recovered from the urine after I.V. injection of the dye. Fraction 1 has an elution peak similar to pure BSP.

were measured but not plotted and roughly parallel the values for glucuronic acid.

In Figure 2 is plotted the optical density of BSP at 578 Mu against successive eluate fractions. The bile-type BSP chromatographs in 4 fractions, 3 of which give different elution peaks than pure BSP. These bile fractions were taken at 20-minute intervals. Fraction 1 consistently chromatographs as does pure BSP.

Figure 3 shows a similar plot of urine-type BSP. The demonstrable elution peaks are usually 3 in number and with the exception of peak # 1 appear in later elution fractions than the large peaks # 3 and 4 of the bile type BSP derivatives. It is not implied that this observation indicates a difference in the

urine and bile-type derivatives as obviously the various constituents of these fluids may produce a variation in the chromatographic pattern.

After passage of the bile containing the excreted BSP through a column of Dowex 50, the eluate was subjected to ascending chromatography using acetone : propionic acid : water (75:25:30) as a moving phase. Two typical BSP spots were localized with an average Rf of .51 and .74—variations depending on temperature. The fast moving spot traveled with an Rf similar to pure BSP. When sprayed with ninhydrin solution, the slower moving spot reacted and became purple. This finding has been repeated in duplicate in 7 patients.

Paper chromatography of the eluate failed to show the presence of ninhydrin positive compounds other than the above BSP fraction. After acid hydrolysis of the Dowex 50 eluate, paper chromatography demonstrated an additional ninhydrin positive compound. This additional material has an Rf similar to taurine and could be this amino acid which has been released from a bile acid conjugate by acid hydrolysis. The possibility that this material is derived from the ninhydrin positive BSP is small as it appears relatively unchanged by hydrolysis. It, however, deserves further study.

Comment

From the above data it is evident that BSP undergoes changes in the process of metabolism and excretion. Recently Rudi Schmid[15] in elucidating the mechanism of bilirubin excretion has focused attention on glucuronide formation. It is also known[16] that phenolphthalein, a dye closely related to BSP, is excreted by animals as phenolphthalein-mono-β-glucuronide. There is, however, nothing to suggest in this study that such a conjugation occurs in the process of transfer of BSP into the bile. Following hydrolysis, glucuronic acid values did not vary with bile-type BSP concentrations but did roughly parallel bilirubin levels.

It has been suggested by Krebs and Brauer[6] in their animal work that the presence of one or more side chains on the phenolic rings explains the presence of BSP derivatives in the bile. The present studies confirm such BSP-derivatives in the human. In addition, the ninhydrin reaction of the derivatives lends credence to the suggestion that a conjugated derivative has been formed. It is interesting to speculate on the significance of the ninhydrin-positive BSP derivative. A blue-colored compound is formed when ninhydrin is heated with alpha amino acids or with peptides or proteins containing at least one free amino and carboxyl group. The molecular structure of BSP does not contain the amino group necessary for the formation of a colored-compound with BSP. Thus, the ninhydrin-positive BSP indicates an addition to the original molecule. On theoretical grounds most of the alpha amino acids can be eliminated as possible conjugates because they lose their ability to react with ninhydrin in the conjugated form. An amino acid conjugate is, however, a distinct possibility and could be ex-

plained by interaction with a portion of the molecule apart from amino and carboxyl groups. Conjugation of BSP with a peptide or a protein would be possible but certainly is not a usual mechanism. Our attempts to identify the ninhydrin-positive compound demonstrated in the hydrolysate of bile-type BSP have as yet been unsuccessful.

It is also interesting to conjecture as to the possible sites on the BSP molecule which would be available for conjugation. Prior work[6] is purported to show that the bromide content of the phenolic ring remains unchanged as does the integrity of the sulfonate groups. It is also significant that the character of BSP as an indicator parallels that of phenolphthalein and depends on transformation from the phenolic to quinoid forms in accordance with changes in pH. Human bile-type BSP retains this ability as an indicator and thus the integrity of one of the phenolic hydroxyl groups as well as the phthalic nucleus must be assumed. By elimination, the remaining phenolic hydroxyl group and the unoccupied positions on the phenolic rings must be held suspect as sites of conjugation.

Further study will perhaps clarify the problem and it is hoped that identification of the excretory mechanism will add to our knowledge of liver metabolism and increase the clinical usefulness of this liver function test.

Summary

To investigate in the human the mechanism by which BSP is excreted into the bile, various studies have been performed on T-tube bile samples following the intravenous injection of the dye. There is evidence to show that BSP undergoes alteration during the process of hepatic excretion. Certain fractions of bile-type BSP are probably excreted in the form of a conjugate. No evidence has been found that the formation of a glucuronide explains the bile-type BSP observed.

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RECURRENT STOMAL ULCER, REFRACTIVE TO REPEATED OPERATIVE PROCEDURES*

An Additional Case of Ulcerogenic Tumor of the Pancreas

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The primary importance of hypersecretion of gastric juice in the genesis of duodenal ulcer is well established. It has been further demonstrated that excessive gastric secretions are implemented chiefly by two physiologic mechanisms; namely, the gastric phase initiated by antral stimuli, and the cephalic phase arising from cerebral stimuli and mediated through the vagus nerve.

Pavlov[1] first noted the importance of the vagus nerve as pertains to cephalic or neurogenic phase of gastric secretion, and this observation has been verified by other investigators[2,3,4]. Following Edkins'[5] discovery of a hormone which was produced by the antral gastric mucosa and which was shown to be a powerful stimulant of gastric secretions, a second important phase of gastric secretion was introduced. This work has been confirmed by Grindlay and Priestley[6] and by Dragstedt[7]. The present generally accepted surgical treatment of duodenal ulcer has evolved from these findings and today comprises either a distal subtotal gastrectomy or bilateral vagus section or some combination of these procedures.

In general, the results following operation for duodenal ulcer have been good, yet in a small group of patients (probably less than 5 per cent) there has been a recurrence of the peptic ulcer in the region of the gastroenterostomy. The development of peptic stomal ulceration following either a subtotal gastric resection or a vagotomy may occur as a complication in any case, and it serves to remind us that the ultimate in surgical treatment of duodenal ulcer has not been found. Furthermore, in the occasional patient, recurrent stomal ulcer develops following repeated surgical procedures including both vagus section and even near total gastric resections. We have encountered two such patients in our clinic which are briefly summarized below.

Report of Cases

Case 1:—J.A.R. (BMH 482241), a white woman, 43 years of age, was admitted to our service on 6 April 1948 because of vomiting of blood and passing

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of tarry stools for several days. She had first noticed epigastric pain and distress with slight nausea and substernal pain one year previously, coming on about six weeks after a total hysterectomy and bilateral salpingo-oophorectomy. A few weeks following the initial onset of the symptoms she had two episodes of passing tarry stools and vomiting bright blood. During the past year she had had several transfusions for this condition at her local hospital.

On examination she was rather pale; there was slight epigastric tenderness; tarry stool was noted on the examining finger on rectal examination. Physical examination was otherwise negative. The hemoglobin was 28 per cent with 1,700,000 red blood cells. Coagulation and bleeding time were normal; urinalysis was normal. Chest roentgenogram and barium study of the colon were normal. A barium study of the stomach and duodenum revealed a large duodenal ulcer. Because of the active bleeding, gastric analysis was not done at that time. On 24 April a subtotal gastric resection was done (65 per cent Polya-Balfour). Two large duodenal ulcers were found in the first portion of the duodenum; a large posterior ulcer about 2 cm. in diameter was penetrating into the pancreas and this seemed to be the source of the bleeding. The patient did well postoperatively, but on 21 June 1948 she was readmitted and a segment of the ileum was resected because of strangulation due to an adhesive band. On 3 September 1948 a follow-up roentgen study of the stomach revealed the stomach was functioning well with no evidence of stomal ulceration at this time. On 7 February 1949 she returned complaining of epigastric and left-sided abdominal pain of about four days' duration. Examination was negative and reexamination of the stomach by barium meal failed to show any defect which might have been considered a stomal ulceration. She was given tincture of belladonna to be taken before meals and advised to return in a few weeks for further study and observation. On 26 February 1950 she returned with complaints of epigastric pain, dyspepsia, fullness after meals and constipation. Roentgen study of the stomach revealed a constant deformity suggestive of a gastrojejunal ulcer. Gastric analysis at this time revealed a free hydrochloric acid of 20 units and a total hydrochloric acid of 38 units. On 23 February 1950 vagotomy through the abdomen was attempted, but because of the extensive adhesions and the inflammatory reaction around the stomal ulceration, it was necessary to abandon the procedure. Thinking possibly there was some obstruction at the stoma, an enteroenterostomy was done. She recovered from this procedure but her symptoms persisted and seemed to grow progressively worse, and on 24 April 1950, a transthoracic bilateral vagus section was done without difficulty. Postoperatively her course was satisfactory, and although she improved somewhat, her symptoms were never entirely relieved. Repeated barium study of the stomach on 29 May revealed a persistent deformity in the region of the gastroenterostomy suggesting persistent stomal ulcer.

She was placed on an ulcer regimen including a modified Sippy diet, antispasmodics, and antacids. In spite of this regimen, she was again admitted to

the Baptist Memorial Hospital on 20 September 1950 as an emergency because of massive upper gastrointestinal bleeding. Although repeated transfusions were given, she remained in a state of shock and died of hemorrhage on 22 September 1950.

Postmortem examination revealed a marginal ulcer at the site of the gastrojejunostomy approximately 2 cm. in diameter with erosion into the splenic artery; also, an enlarged lymph node 3 cm. in diameter was found lying in the region of the celiac axis. The capsule appeared to be thickened, and on cut surface this node appeared to be hemorrhagic and soft and scraped with ease. Microscopically, it was described as follows, "The pattern is that of interlacing ribbons and cords of cells bordering thin-walled vascular sinuses engorged with blood. These cells are uniform in size. The nuclei are relatively large, round to oval in shape, and are rather vesicular with small nucleoli often visible. Mitotic figures are not seen. The pattern of this tumor is consistent with islet cell adenoma." There were no other significant findings.

Case 2:—P.S. (BMH 42825), a white female 54 years of age, was admitted to our service on 8 July 1949 with a history of stomach trouble dating back 15 years. The symptoms were those of dull, boring epigastric pain with food relief. Five years previously she had had her gallbladder removed at which time an active duodenal ulcer was noted. During the past two years the symptoms of pain and epigastric distress became more marked and more persistent, and during the past two months, in addition to her previous symptoms, she developed vomiting and episodes of acute pain. Also, there were attacks of diarrhea and during the past five years there was a weight loss of about 35 pounds.

Her past history revealed that she had had an appendectomy at age 25, a total hysterectomy and bilateral salpingo-oophorectomy at age 40, and cholecystectomy at age 50.

Physical examination revealed a thin, frail, white woman with evidence of weight loss. Except for epigastric tenderness, the physical examination was negative. Barium studies of the upper gastrointestinal tract showed a marked deformity of the first portion of the duodenum suggesting duodenal ulcer with partial obstruction. Gastric analysis revealed total hydrochloric acid of 98 units.

On 11 July 1949 a subtotal gastric resection (65-70 per cent Polya-Balfour type) was done for a large, subacute, partially obstructing duodenal ulcer. Her postoperative course was uncomplicated, and she was dismissed from the hospital in the usual time. On 5 August 1949 she suddenly developed acute epigastric pain and vomited blood. At this time the hemoglobin was reported as 48 per cent with a red blood cell count of 3,000,000. Examination revealed marked tenderness in the epigastrium; however, there were no palpable masses. Barium meal was not entirely satisfactory, but did show a hypermotility of the small bowel.

On 11 August 1949 she again had a sudden onset of acute epigastric pain which was followed by mild shock and rigidity of the abdomen. At this time she was reoperated and a large, acute, perforating gastrojejunal ulcer with a gastrojejunocolic fistula was found. The stomach was resected again. The jejunum was closed and the gastroenterostomy reset 12 inches distally. The colon was repaired and a right transverse colostomy was done. The immediate postoperative course was uncomplicated. On 1 September 1949 the patient developed tenderness in the left upper quadrant and temperature elevation up to 103° F. The hemoglobin was 28 per cent at this time, and the white blood cell count was 19,000. There was very little response to the antibiotic therapy and with development of a mass in the left upper quadrant, a subcostal incision was made with drainage of a subphrenic abscess. Her progress was rather slow, and although she was able to take a modified postgastrectomy diet, she remained weak and anemic, and failed to regain any strength or weight in spite of repeated blood transfusions and protein hydrolysates intravenously. At times there appeared to be gastric contents drainage through the stab wound in the left upper quadrant and because of her continued downhill course, she was reexplored on 9 November 1949. A gastrojejunal fistula opening into the abscess in the left upper quadrant was noted. A small portion of the stomach was again resected leaving only approximately an inch and a half cuff of the stomach. The abscess cavity was drained.

Again, a few days after operation, gastric contents appeared at the drainage site. The postoperative course was relentlessly downhill, and she died on 1 December 1949.

Postmortem study revealed evidence of ulceration at the site of the gastroenterostomy with disruption of the suture line at this point. In addition, an abscess was noted in the left upper quadrant and there was also mild peritonitis. No other significant findings were recorded in the protocol.

Comment

According to Gossett[8], Braun, in 1899 (first reported the finding of a jejunal ulcer developing one year after a gastroenterostomy. Although the incidence of stomal ulceration following present day surgical procedures is probably less than five per cent, it is a most serious and disabling complication. More disturbing is the rare case which does not respond to secondary operative procedures designed to relieve this complication. Deaver[9] referred to such a patient in his personal experience as follows, "It may be of interest to mention that I have one patient upon whom I have operated three times for marginal ulcer and who now, I am quite sure, has a fourth one. This is in keeping with what I have always maintained, that some individuals have an *ulcer habit* which it seems nothing will cure." Priestley[10] states that the occasional patient may have another ulcer even after gastric resection and vagotomy, and in one patient who

had had five previous operations for peptic ulcer, a total gastrectomy was finally necessary.

The two cases presented here were most disturbing and at the time the refractory aspects were inexplicable. Following the initial report by Zollinger and Ellison[11] we realized that the first case fit into the category of ulcerogenic pancreatic tumor. It is assumed that the primary tumor in this case was in the pancreas (most likely overlooked during the postmortem examination), and that the node at the celiac axis was a metastatic lesion.

The etiologic facts are not so apparent in the second case. Although it is well known that wound healing is poor in the malnourished, protein depleted patient (as was the situation with this patient), there was no evidence of delayed healing of the abdominal incisions. The infection following the second operative procedure, no doubt, was an additional deterrent to healing. The role of the central nervous system aberrations in the formation of peptic ulcers has long been recognized even though obscure; the import of psychic disturbances in producing acute peptic ulceration has been emphasized by Hoffman[12] and Kraines[13]. This patient was a highly nervous, pent-up, tense individual, and her symptoms became more severe following total hysterectomy and bilateral salpingo-oophorectomy. It is possible that such states are purely coincidental observations and have no causal relationship.

In addition to influences well known to be mediated through the vagus nerve, it has been shown by Porter, et al[14], using monkeys for experimental stimulation studies, that there is a humorally conducted response arising in the posterior hypothalamus. Furthermore, in recent years, we have seen clinically the ulcerogenic effect of corticosteroid therapy, and although much study and research has been done on the action of these agents, the precise mode of action is not known—it is not abolished by vagotomy, anticholinergic drugs, or gastric antral resection[15].

Summary and Conclusions

Duodenal ulcer as a disease is a composite of interrelated physiologic, biochemical and psychic disturbances. The efforts of the surgeon to relieve the symptoms by antral gastric resections and/or vagotomy have been successful except for a small percentage of patients. The recent reports of finding of certain endocrine tumors associated with the refractive ulcer patient marks another major advance in the understanding of the ulcer problem.

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ACUTE INTERMITTENT HEPATIC PORPHYRIA A CAUSE OF UNEXPLAINED ABDOMINAL PAIN*

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Recently, we have had the opportunity of studying a patient with proven *porphyria hepatica*, acute intermittent type. Our case report deals with the clinical aspects of porphyria, historical approach, porphyria classification and terminology, diagnosis, pathogenesis, pathological picture, prognosis and recent therapeutic considerations.

Our case is presented in some detail because of its diagnostic difficulties and unusual manifestations.

Case Report

A 47-year old Danish carpenter was admitted on the orthopedic service of the Santa Barbara Cottage Hospital on 5 March 1956, because of a 12-year history of low back pain.

On 7 March 1956, orthopedic surgery was performed with a preoperative diagnosis of herniated intervertebral disc and unstable low back. Under general anesthesia a laminectomy was carried out at the 5-4 level and the 4-3 level, sodium pentothal being used to introduce anesthesia. A tremendous herniation of disc material was encountered at the 4-3 level and this was removed. A spine fusion was then carried out, including the 3rd, 4th and 5th lumbar area. The wound was then closed and the patient returned to bed in good condition.

Pathologic sections were reported on 9 March 1956, as follows: "Gross description: The specimen received previously fixed in formalin consists of fragments of fibrillar, gray-white fibro-cartilage together weighing four grams. Microscopic diagnosis: Chondromalacia of nucleus pulposus."

The patient was seen in consultation by the author on 12 March 1956, five days postoperative. Since his surgery the patient had complained of severe generalized abdominal pain not relieved by frequent injections of various barbiturates, morphine and demerol. He complained of marked pain and cramping all over the abdomen, severe numbness, tingling and aching of the arms and legs; had severe nausea with frequent emesis day and night with marked constipation.

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Past history:—The patient weighed 150 pounds five years ago but had steadily lost weight to 115 pounds before his present hospital admission for orthopedic surgery. He had noted gradual weight loss, marked fatigue and exhaustion unusual for a formerly industrious, stable Danish carpenter, his wife said. The wife had noted recent peculiar psychoneurotic manifestations, almost a delirium, and the local physician urged psychiatric consultations several times. The patient mentioned intermittent bouts of severe colicky pain in the abdomen recently before admission and had noted a peculiar pigmentation of his skin and McBurney appendical scar.

No history of exposure to lead, chloroform or heavy metal was obtained. There was never a history of photosensitivity, and as a carpenter he was tanned from the outdoor California sunshine of the hot Santa Ynez Valley.

An appendectomy was done in 1929 for severe lower abdominal distress, but the patient stated that he had severe abdominal pain after surgery while still in the hospital, worse than before surgery.

The family history is not adequate as no siblings were available for study. His father died of "old age" and his mother of tuberculosis in Denmark. Two twin brothers, age 44, are alive in Denmark and they have apparently had indigestion and abdominal distress. A sister, age 50, is living and well in Denmark and another sister, age 49, is living and well in the East.

Physical examination:—On 12 March 1956, an acute and chronically ill 47-year old male was seen lying uncomfortably on a Stryker orthopedic frame complaining of severe pain in the abdomen, arms and legs. The blood pressure was 120/80, pulse was 110, respirations 16 and temperature 99.0°.

The skin showed marked dehydration. A dirty brown pigmentation was seen on the exposed areas of the arms and legs, and the appendectomy scar was deeply pigmented. No India ink spots, buccal or gum pigmentation was seen.

The pupils were miotic from opiates and the fundi were normal, showing no arteriolar attenuation. The tongue was dry and parched from dehydration. The heart showed a persistent sinus tachycardia of 110 to 120; but no murmurs, gallop or friction rub was heard.

The abdomen was soft but tender with easily palpable cecum, and dilated loops of small bowel were visible. The liver and spleen were not palpable. Rectal examination disclosed no feces or impaction although the patient had no enemas or laxatives since surgery. Neurologic examination showed a hyporeflexia, the right ankle jerk being absent.

Laboratory studies:—Because of his most stormy postoperative course with fever, persistent tachycardia, generalized abdominal pain and severe psychoneuroses bordering on delirium, a clinical diagnosis of hepatic porphyria was suspected. This was confirmed by positive screening Schwartz-Watson tests for

porphobilinogenuria[6] on 26, 27, 28 and 29 March. Also, a marked red fluorescence in ultraviolet of extraction of an aliquot of urine was obtained. The nurses' notes described red urine on several occasions.

A 24-hour urine was examined on 28 March for quantitative porphyrins. The coproporphyrins were elevated to 263 mcg., the normal being less than

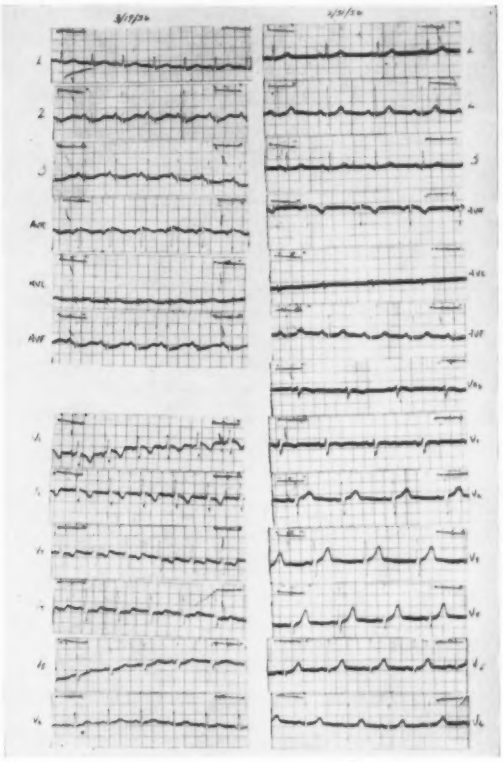

Fig. 1a Fig. 1b

Fig. 1a—ECG of 17 March 1956 showing deep inversion of the T waves in V_1, V_2, V_3 and a diphasic T in V_4, consistent with anteroseptal ischemia.

Fig. 1b—ECG of 31 May 1956 showing normal V leads in V_1, V_2, V_3, V_4. ECG now within normal limits as compared with tracing of 17 March 1956.

120 mcg. Uroporphyrins were elevated to 1,840 mcg., normally none being detected in urine. The 24-hour urine was also strongly positive for porphobilinogen.

Urine samples left to stand overnight developed a port wine to black color on all occasions. The admission red blood count was 5,300,000 with 16.4 gm. of

hemoglobin. The white blood count was 5,700 with 42 segmented forms and 39 lymphocytes. Bromsulfalein retention of 15.5 per cent was seen in 45 minutes after 5 mg./K. The normal level is 4 per cent in 45 minutes. Serum amylase was elevated to 400 and 457 S units on two occasions, but large doses of opiates had been given (normal 80 to 150 S units). Serum lipase was 0.95 units and 0.93 units (normal 1 to 1.4 units). Total serum bilirubin was 0.76 mg. per cent (normal 0.30 to 1.0 mg. per cent); 30 minutes direct bilirubin 0.5 mg. per cent (normal 0.24 to 0.70 mg. per cent); indirect 0.26 mg. per cent (normal 0.06 to 0.80 mg. per cent); 1 minute direct bilirubin 0.29 mg. per cent (normal 0.06 to 0.25 mg. per cent). Urine urobilinogen was 1.6 mg./100 ml. (quantitative urine).

Urine showed no growth of organism on culture, and routine urinalysis was normal. The clotted blood peripheral blood *L.E.* test was negative for systemic *lupus erythematosus*. Blood glucose was 91 mg. per cent, blood N.P.N. was 28 mg. per cent, CO_2 combining power was 25.6 mEq./l., serum sodium was 138 mEq./l., serum potassium was 4.0 mEq./l. VDRL test for syphilis was negative. The Thorne ACTH test was normal, fasting eosinophil count being 543 cu.mm., dropping to 22 eosinophils cu.mm. after 25 mg. ACTH.

A portable chest film on 17 March 1956, showed no evidence of pulmonary or pleural disease. The heart, mediastinal and hilus shadows were within normal limits. There was some calcification in and about the right hilus.

The electrocardiogram of 17 March 1956, had auricular and ventricular rate of 104, PR interval of 0.13 seconds, QRS of 0.09 seconds, QT interval of 0.40 seconds. The P waves in leads II and III showed slight peaking. The heart was in a semivertical position electrically. Deep inversion of the T waves in V_1, V_2, V_3 and a diphasic T in V_4 was evident. Electrocardiographic diagnoses included: 1. sinus tachycardia, and 2. abnormal myocardium consistent with anteroseptal ischemia.

Anteroposterior and posteroanterior studies of the lower chest and abdomen by x-ray on 21 March 1956, showed a considerable amount of fecal material and gas scattered in the colon. The findings were not characteristic of intestinal obstruction. No opaque calculi were seen, and there were no abnormal soft tissue shadows or pancreatic calculi seen.

X-rays of the gastrointestinal tract were made on 24 March and 26 March 1956, under great difficulty due to a recent laminectomy and back fusion.

Fluoroscopically the esophagus was negative and studies following fractional and full barium meals showed no abnormality in the walls or mucosa of the stomach, duodenum or upper small intestine. At three hours most of the barium was in the jejunum and had left the stomach. There was, in spite of attempted preparation for three days with castor oil, a considerable amount

of fecal material in the right colon and also much gas and fecal material in the left colon.

Colon study by barium enema administered under fluoroscopic control and film studies before evacuation showed a large caliber atonic colon, dilated throughout. No organic lesion was identified in the colon. Cholecystograms showed a normal functioning gallbladder without gallstones, and a large amount of barium remained in the colon from previous gastrointestinal studies.

Course: — We were unable to control the patient's nausea, vomiting and severe abdominal distress with demerol, morphine, thorazine, etc. All barbitu-

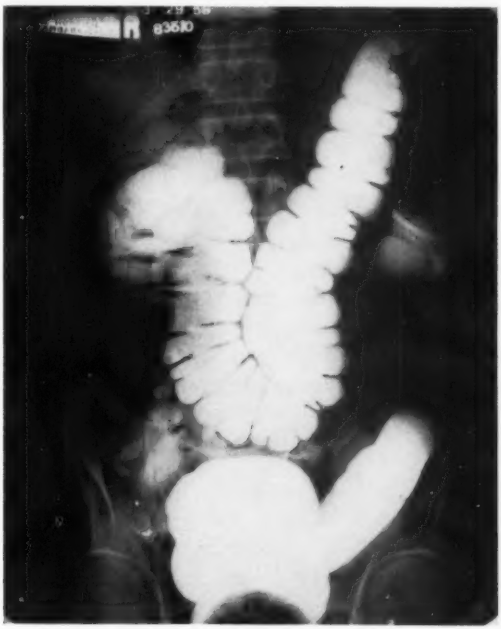

Fig. 2—Colon examination of 29 March 1956, showing a large caliber, atonic colon, dilated throughout, characteristic of acute hepatic porphyria.

rates were promptly stopped after notifying the orthopedic service. Intravenous nourishment was necessary for a prolonged period. Repeated chemistries showed no serious electrolyte problems.

Massive doses of Vitamin B_{12}, B-complex, neostigmine, and calcium gluconate were of no therapeutic value. Striking relief in all symptoms occurred after giving 20 units of ACTH in 1,000 c.c. 5 per cent glucose in water for several days slowly over an eight-hour period. Gradually, due to the striking

relief of all his symptoms with intravenous ACTH, he was placed on depot ACTH gel, 40 units intramuscularly daily. The severe abdominal pain, neuritis, delirium, constipation, tachycardia and fever subsided under corticotrophin therapy. Gradually, ACTH was reduced and withdrawn without relapse.

He was discharged completely asymptomatic on 7 April 1956, on a high carbohydrate, high protein diet, multivitamins and thorazine, 25 mg. four times daily, the latter helping him greatly in our opinion.

The patient reported to our office on 27 April 1956, asymptomatic. His appetite was normal, he had no gastrointestinal complaints, normal daily stool, but still had a mild exhaustion state. His weight had climbed to 126 pounds, blood pressure was 90/60, pulse 68, temperature 98.6°. Physical examination was normal. A routine urine on this date again showed a strongly positive Schwartz-Watson test. The urine of his four children was checked for porphobilinogen and reported negative. He was advised to continue all measures.

His next office visit was on 31 May 1956. He felt fine with no complaints. Appetite was excellent. He had no gastrointestinal complaints and normal daily stool. Weight had risen to 139½ pounds, and physical findings were unchanged.

An electrocardiogram on 31 May 1956, showed a rate of 72 with normal sinus rhythm. QRS was .08 seconds, PR 0.16 seconds, QT .36 seconds. P waves were upright and normal. QRS complexes were upright in all three limb leads with a tiny q and s in leads II and III and a tiny s in lead I. The heart was in a semivertical position electrically and the V leads were now normal. Electrocardiographic conclusions were: "Electrocardiogram within normal limits. Compared with the tracing of 17 March 1956, the ST segment depression has disappeared in V_2, V_3, V_4 and T waves are now normal."

Routine Schwartz-Watson test for porphobilinogen on 31 May 1956, was again strongly positive. Hemoglobin was 13.4 gm., red blood cells 4,510,000, and white blood cells 7,700 with 62 neutrophils, 27 lymphocytes, and 8 monocytes. Sedimentation rate was elevated to 33 mm. fall in one hour (normal range 0 to 9 mm.).

The quantitative studies on the 24-hour urine on 2 June, 1956, were again interesting in spite of his asymptomatic course. Quantitative coproporphyrins were 274 mcg./24 hours, the normal being up to 120 mcg. Uroporphyrins were elevated to 485 mcg./24 hours, the normal being 0. Quantitative porphobilinogen was again positive.

The patient has reported to us every three months faithfully through 1956, 1957 and 1958 and has been essentially asymptomatic. Occasional periumbilical abdominal distress is relieved by thorazine, 25 mg. every 12 hours. Urines are positive for porphobilinogen on each occasion and turn port wine or black color on standing overnight. Present weight is 137 pounds on 29 March, 1958,

and patient is asymptomatic. He takes thorazine, 25 mg. every 12 hours. Electrocardiogram 25 January 1958, is normal, a sinus bradycardia being present. A 24-hour urine for porphyrin study 28 April 1958, shows coproporphyrin 332 mcg./24 hours; the normal is up to 120 mcg. Uroporphyrin is 578 mcg./24 hours; the normal is none. Porphobilinogen is positive; normal is none.

The patient was advised to continue his diet and vitamins, and thorazine was continued intermittently. He will be followed periodically and will avoid all barbiturates, solvents, oil paints[4], alcohol, heavy metals, sulfonamide, etc. So far his progress has been striking to all who have seen him.

Comment

History of porphyria: — The history of porphyrin metabolism is most interesting. Gunther[5] states a reddish pigment formed by sulfuric acid on hemoglobin was produced in 1841 by Scherer. Baumstark[6] found similar pigments in a leper, and Garrod[7] described hematoporphyrins in the urine in health in small quantities and larger amounts in disease in 1892. Gunther[5] mentioned red urine pigments as a cause of anomaly of pigment metabolism which he called hematoporphyria.

Modern description of porphyrins dates from 1915, Hans Fischer[8] reporting the well-known congenital porphyria of Petry, now recognized as erythropoietic porphyria. In 1924 Fischer[9] isolated the red-brown uroporphyrin and coproporphyrin pigments, showing that patients with porphyria never excrete hematoporphyrin, which is a product of the laboratory, not the body.

The porphyrins classically have a basic four pyrrole ring structure connected by methene bridges[10] and found in the animal and plant environment. Individual porphyrins differ depending on the eight possible side chains, each porphyrin having several possible stereoisomers. Chlorophyll has actinoporphyrin as a pigment, and blood pigment has protoporphyrin. Ingested plant and animal tissues furnish coproporphyrin and uroporphyrin, both being excreted in feces and urine[10], no scientific facts being certain that they are produced from hemoglobin destruction.

Types I and III isomers of these porphyrins occur in nature, the liver being the chief excretory route. Ordinarily 10 to 100 mcg. of coproporphyrin are excreted via the kidneys and 150 to 300 mcg. in the stool in 24 hours, type I predominating over type III.

The type I and type III isomers are found by chemical fractionation and melting point analysis. Metalloporphyrin complexes[11] are ingredients of many chemical substances such as cytochromes, catalases and chlorophylls.

According to Sunderman[11], two molecules of S-aminolevulinic acid, a succinyl derivative synthesized from glycine or acetate through the Krebs' cycle

condense to form the pyrrole porphobilinogen. Four molecules of porphobilinogen condense to make uroporphyrin III by an indefinite association. Recent work suggests that coproporphyrin III may be formed directly from porphobilinogen. Coproporphyrin III is then transformed to protoporphyrin III, the latter compound uniting with ferrous iron to make heme, the prosthetic group of catalase, myoglobin, etc.[12]. The metabolic pathway, Sunderman says, is similar for series I porphyrins.

When large quantities of uroporphyrins are excreted in the urine, porphyria is present. Porphyrinuria means that coproporphyrins predominate in the urine rather than uroporphyrins. It is usually a secondary manifestation in humans.

Some blood relatives of porphyria patients remain in good health but excrete pathologic quantities of urinary porphyrins – a latent trend[4].

In 1954, Watson and Schmid[13] classified all porphyrias as erythropoietic and hepatic on the basis of tissue porphyrins. The bone marrow is the apparent site of the pathologic production of uroporphyrin in erythropoietic porphyria. The liver produces the abnormal amounts of porphobilinogen and uroporphyrins in hepatic porphyria.

Congenital (erythropoietic) porphyria is usually first seen by the pediatrician or dermatologist as it begins in childhood. It represents an inborn error of metabolism; and there is a persistence of fetal pyrrole metabolism, being inherited as a recessive Mendelian characteristic and more common in male children[10].

This entity shows large amounts of uroporphyrin and coproporphyrin type I in the urine, increased blood porphyrins, pigment discoloration of teeth, bones and skin and a cutaneous erpution with light sensitivity. It is usually a benign disease[14]. Urine color varies from black, red to pink. If the urine is heated or acidified, it will become darker and color changes are prevented by an alkaline urine.

The pink enamel of the teeth and bones of the hands can be seen pigmented by transillumination. The skin displays bullous-vesicular lesions occurring usually on the face, hands, neck; and with healing there is scarring and hyperpigmentation. Hypertrichiasis and enlarged viscera such as liver and spleen may be seen. No porphobilinogen is found in the urine, and the Schwartz-Watson test is negative. A fluorescence of normoblasts in the bone marrow may be seen.

All sunlight should be avoided, and perhaps large doses of liver extracts and vitamins decrease porphyrin excretions. Splenectomy may result in temporary improvement[15].

Acute hepatic porphyria is really a chronic illness with relapses and remissions for months to 25 years. It can be familial, and it has not been pos-

TABLE I

RECENT CLASSIFICATIONS OF PORPHYRIA

A. Gunther[1] (1922).
   1. Genuine acute hematoporphyria.
   2. Genuine chronic hematoporphyria.
   3. Toxic hematoporphyria.
   4. Congenital porphyria.

B. Micheli and Dominici[2] (1931).
   1. Idiopathic porphyria.
      a. Abdominal form.
      b. Nervous form.
      c. Cutaneous form.
   2. Toxic porphyria.

C. Waldenstrom[3] (1937).
   1. *Porphyria congenita* (Gunther's disease).
   2. *Porphyria cutanea tarda.*
   3. *Porphyria acuta.*
      a. Latent porphyria.
      b. Pure abdominal form.
      c. Pure nervous form.
      d. Classic acute porphyria with colic and palsy.
      e. Comatose form.

D. Watson[4] (1954).

E. Sunderman[11] (1955).
   1. Erythropoietic porphyria.
   2. Hepatic porphyria.
      a. Paroxysmal hepatic porphyria.
      b. Photosensitive hepatic porphyria.
      c. Combined paroxysmal and photosensitive hepatic porphyria.

Types of Porphyria	Clinical Syndrome			Tissue Containing Major Concentration of Porphyrins
	Abdominal and Neuropsychiatric Symptoms	Cutaneous Symptoms	Porphobilinogenuria	
I. *Porphyria erythropoietica* (Congenital porphyria)	0	+	0	Bone marrow
II. *Porphyria hepatica*				Liver
a. Acute intermittent porphyria	+	0	+	As precursors
b. *Porphyria cutanea tarda*	0	+	0	Preformed
c. Mixed porphyria	+	+	+	Preformed and/or as precursors

sible to correlate the clinical syndrome with a definite pattern of porphyrin excretion[16]. Hepatic porphyria, more common in women than men, is seen most often in second to fifth decades[10] Bizarre symptoms with abdominal distress, psychoneuroses, neuritis and weakness may be noted with history of black or red urine excretion in the past.

Perhaps the patient had recent surgery with barbiturate sedation or had injected sulfonal, trional, alcohol or lead. Nausea, emesis and obstipation are common. Hepatic parenchymal damage is seen; and x-rays show a huge, atonic colon.

Landry's ascending paralysis is seen at times[17], and bulbar palsy may be the cause of death. Spotted pigmentation of the skin excluding the buccal mucosa is common. Transient electrocardiographic changes during the acute phase have been seen sometimes with inverted T waves, elevated ST in lead I and slurring of the ST in lead III—nonspecific changes[17]. These changes of transient myocardial ischemia are from coronary artery spasm[20]. Leucocytosis may be found.

The diagnosis of acute hepatic porphyria will be made only if it is considered and supported by the Schwartz-Watson test. Consider it in any vague case of severe bizarre abdominal distress with central nervous system association, especially if a urine setting overnight turns dark.

A differential diagnosis is difficult. Certainly a surgical belly is simulated with symptoms of nausea, emesis, ileus, constipation. The abdomen characteristically remains soft, however. Acute appendicitis, pancreatitis, ileus, intestinal obstruction, ulcer and biliary disease are a few surgical possibilities. Addison's disease and Guillain-Barre syndrome may also be simulated, as well as many other acute medical emergencies.

The cause of the many and varied symptomatology remains unknown. Porphyrins may act on smooth muscle of the intestinal tract, and porphyrins injected intravenously or locally interrupt the normal rhythmic contractions which atropine will not restore. Meissner's plexus may be inhibited by porphyrins[18]. Porphyrins can have a lethal effect on the nervous system, multiple neuritis occurring after the hematoporphyrin (photodyn) has been ingested[19]. Attenuation of retinal arterioles has been described[20].

Pathological studies may be vague. Patchy degeneration of peripheral nerves and anterior horn cells is seen. Sympathetic ganglion cells may show pigmentation, vacuolization, and the cortical cells may show pyknosis; and amorphous pigment can be seen, iron and noniron containing. Uroporphyrin and coproporphyrin is demonstrated in the cells of the nervous system[21]. The liver may be enlarged with cloudy swelling to control necrosis and spleen can be enlarged. Renal glomeruli may show degenerative changes. Muscle atrophy

may be seen and cardiac muscle shows hemorrhage into interstitial spaces and fatty degeneration of muscle[22].

The urine is dark brown, "Coca-Cola" colored or port wine color. It usually contains type III isomers of both uroporphyrin and coproporphyrin, the former as a zinc complex. There is also increased porphobilinogen on oxidation[10]. Uroporphyrins I or III may predominate in the urine[11].

Prognosis should be cautious. Of 100 patients observed by Waldenstrom[3], 20 died within one year following the appearance of the disease clinically, 2 lived 8 years and of 12 living patients, 1 lived 27 years. With neurologic sequela and bulbar palsy with respiratory failure, the mortality may reach 90 per cent[35].

Therapy remains nonspecific. Toxic agents such as barbiturates, sulfa, alcohol, lead, etc., should be avoided.

ACTH and cortisone are useful at times, but not always curative[23]. Janoff[24] obtained a dramatic remission in a case of mixed porphyria within 24 hours. A favorable response was found in only 10 of 22 cases reported by Olson and Stiles[25].

Other therapeutic agents have been tried with variable results including calcium salts[26], Vitamin B_{12}[13], prostigmine[27], and atropine sulfate[28]. Various other drugs such as priscoline, novocain, trasentine and glyceryl trinitrate have given poor results on the whole[29].

Watson[30] has shown that chlorpromazine is the best agent available for acute porphyria, and we would concur. Melby also has shown its value[31]. The latter has shown that chlorpromazine is more likely to cause a remission than any other drug by ameliorating autonomic disturbances. It may be necessary to give 100 mg. six times daily, but later it may be reduced or discontinued. A small maintenance dose may be necessary as with our case. These patients must also avoid nervous stress as the latter may precipitate acute porphyria. Possibly, says Watson, chlorpromazine removes pain, allays tension, interrupts a vicious cycle and allows spontaneous remission. If the patient avoids chemical exposure, barbiturates, nervous tension, remission may last for more than ten years.

Recently, Peters and group[32] summarized the favorable effect of chelatin in 14 of 21 acute porphyria patients with BAL and EDTA with heightened excretion of zinc during chelatin suggesting rapid neutralization of heavy metal toxicity by binding and removing from vulnerable enzyme systems.

The nutritional state of the patient must be watched carefully, especially if liver disease is present. With onset of neurologic palsies, bulbar weakness may develop and a tracheotomy and respirator must be used.

Photosensitive hepatic porphyria (*porphyria cutanea tarda*) is characterized by its greater prevalence in men and marked photosensitivity with vesicular lesions. Abdominal distress and neuritis may be seen. Urine and feces may show large amounts of uroporphyrins and coproporphyrins, and porphobilinogen is usually not found[33].

The prognosis is favorable. Treatment is the same as for the hepatic acute porphyrias.

Mixed type: – Here photosensitivity combined with abdominal and neurological signs. This form may be a transition between the paroxysmal and photosensitive type[11].

Porphyrinuria: – Coproporphyrin I and III are found in urine normally in small amount, 0-189 mcg. Our classification of various conditions with increased excretion of urinary coproporphyrins is as follows:

1. Metals – lead, arsenic, mercury, bismuth, copper, iron, gold, silver, zinc, phosphorus.
2. Sedatives – Veronal, sulfonal, barbiturates.
3. Alcohol.
4. TNT, CH_3Cl and $C Cl_4$.

Hypermetabolism:

1. Fever.
2. Thyrotoxicosis.
3. Exercise.

Hepatic Disease:

1. Cirrhosis.
2. Hepatitis.
3. Carcinomatosis.

Blood:

1. P.A.
2. Hemolytic anemias.
3. Hemochromatosis.
4. Leukemia and Hodgkin's disease.

Hypovitaminosis:

1. Pellagra.
2. Ariboflavinosis.

Porphobilinogen

Porphobilinogen, a pyrrole precursor of porphyrins, is found in urines of people having hepatic porphyria. The preparation resulting from porphobilinogen with Ehrlich's reagent is easily separated from urobilinogen aldehyde and indole aldehyde by insolubility in chloroform[34].

The concentration of porphobilinogens often increases on standing, and a red nonporphyrin pigment may cause the urine to show a "Coca-Cola" color. This latter pigment is porphobilin.

Schwartz-Watson Test for Porphobilinogen

The Schwartz-Watson porphobilinogen test is a simple and rapid test that can be run in any small laboratory[35]. Three ml. of Ehrlich's aldehyde reagent (0.7 gm. of paradimethylamidobenzaldehyde, 150 ml. of concentrated hydrochloric acid and 100 ml. of distilled water) is mixed with 3 ml. of urine. To this mixture is added 6 ml. of a saturated solution (aqueous) of sodium acetate. If a pink or cherry red color develops, 3 ml. of chloroform is added and the tube is shaken for two minutes and permitted to settle for some minutes to allow separation of the watery and chloroform portions. Persistence of the pink or cherry red color in the aqueous supernatant shows the presence of porphobilinogen

Welcker found no false positive reactions on 1,000 patients, and Waldenstrom and Vahlquist concur. Watson[13] on rare occasions has found porphobilinogen and uroporphyrin in polio, cirrhosis, Hodgkin's disease and from urine of infants who had ingested beets or crayons.

Summary and Conclusions

The subject of acute intermittent hepatic porphyria has been presented. Barbituric acid derivatives may act as a precipitory factor in an acute episode, especially with surgery and trauma. It is a chronic disease with remissions and relapses over a period of many years.

The diagnosis will be made only if this unusual entity is considered in all cases of unusual abdominal distress, especially if associated with central nervous symptoms, neurological or psychiatric.

The Schwartz-Watson test for porphobilinogen and thus for hepatic porphyria is cheap, simple to carry out in the smallest laboratory, and rapid. It

is quite accurate; Hammond and Walker found no false positive tests on 1,000 urine specimens[34]. Watson has mentioned only 11 possible false positive tests in 15 years in his laboratory in cases of cirrhosis, Hodgkin's disease, polio, etc.[13]. This test should be done in all bizarre abdominal complaints not easily diagnosed.

Porphyria is not as uncommon as formerly supposed, and more cases are being reported as the Schwartz-Watson test is utilized.

Just as the serum amylase test has been used for many acute abdominal complaints not easily diagnosed, the Schwartz-Watson test for hepatic porphyria should likewise be considered.

ACKNOWLEDGMENT

Appreciation is gratefully extended to Dr. Walter C. Graham of the Department of Orthopedics, Santa Barbara Medical Clinic and Cottage Hospital, and Miss Laurie Johnson and Miss Janet Ulmer who faithfully typed all manuscripts and helped in editing this case report.

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NORETHANDROLONE IN THE POSTGASTRECTOMY STATE; EFFECT ON WEIGHT LOSS*

(With Observations on Its Value in Other States of Inanition)

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Chronic weight loss following subtotal gastric resection for peptic ulcer is a distressing complication which presents a pressing challenge to the clinician. Approximately 50 per cent of such patients with or without vagotomy develop a significant weight loss or fail to regain normal weight. It has been estimated that 10 to 15 per cent have serious nutritional problems[1], and it has been considered that these nutritional difficulties are not due to inadequate dietary intake but may be the result of a defect in digestion.

Therapy directed to this problem has been often disappointing. The need for a more effective method of treatment prompted the decision to evaluate the use of Norethandrolone‡ (17 alpha-ethyl-17-hydroxy-norandrostenone), a synthetic analogue of the steroids. This hormone has been shown to produce an anabolic effect in cases of severe protein breakdown[2]. A negative nitrogen balance is reversed in the postoperative state following burns and abdominal surgery. Biochemical balance studies in conditions resulting from increased protein catabolism indicate that this compound is effective on a short-term basis following surgery in effecting weight increase.

A disturbed absorptive capacity of the digestive tract for protein may hypothetically occur in patients with subtotal gastric resection and in those with short-circuiting intestinal surgical procedures with complicating marked weight loss. We proposed to test the probable usefulness of this agent in a fairly long-term clinical study with respect to permanent weight gain and increased appetite.

It was found feasible, in addition, to employ the drug in patients with undue chronic weight loss of undetermined origin and following various gastrointestinal diseases or loss of absorptive capacity due to extensive surgery. This report concerns itself with such a study on 28 cases carried out over a one-year period under out-patient clinic and private practice conditions.

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Material and Methods

The cases studied fell into five groups: 1. patients with symptoms of the dumping syndrome following subtotal resection with profound chronic weight loss, 2. a similar group without active dumping syndrome symptoms, 3. weight loss of undetermined etiology, 4. patients with chronic gastrointestinal disease such as chronic ulcerative colitis, regional ileitis, or loss of intestinal absorptive capacity as a result of widespread surgical removal of the small bowel, 5. inanition of carcinomatosis secondary to gastrointestinal or other malignancy.

Norethandrolone was administered orally in doses of 10 mg. three times daily after meals for a period of six weeks; in some cases it was increased to 50 mg. daily for months when necessary. Parenteral injection was additionally employed in three cases. Attention was paid to the presence and rapidity of weight gain, change in appetite, sense of well being, and the degree of permanence of the weight increase when the drug was discontinued.

Follow-up information was obtained one year later in some instances. The comparative effect of previous therapy on weight was noted when available.

Since Norethandrolone is closely related in chemical structure to Norethynedrol*, the so-called normalizer of menstrual flow, we looked for possible hormonal cyclic imbalances. Edema, disturbances in the menstrual cycle in women, and other side-effects were noted. Other therapy given concurrently was noted.

Results

The cases of gastric resection ranged from 38 to 67 years of age; seven were male, six were female and the average was 55 years. In the six cases with weight loss of undetermined origin, the average was 45 years with a range from 21 to 75 years; in those with chronic gastrointestinal disease the average was 33 years.

1. Gastric resection cases:—Thirteen cases with gastric resection were studied. Nine had active symptoms characteristic of the "dumping" syndrome while the drug was taken. One case in the first 24 hours of administration developed a marked exacerbation of the abdominal pain, dyspnea, weakness and diarrhea. The drug was discontinued. Two other cases refused the medication but we continued to observe them. One lost 15 pounds in one year and the other gained five pounds in two months with treatment consisting of frequent small feedings, sedation, anticholinergic drugs and atropine.

In the remaining ten cases, of which one received two separate courses, four gained from eight to eleven pounds when given the drug for four to six weeks, two gained from five to six pounds. In two patients with a total of three

*Enovid (G. D. Searle & Co.)

courses there was a two- to three-pound increase and two remained stationary. In three cases in this group, standard treatment consisting of small frequent feedings, atropine, restriction of fluids, postprandial rest and sedation carried out at later dates was also followed by weight gain. In one (E.P.) ten pounds were gained in three months; in the second (S.L.) ten pounds in seven weeks and in the last (A.L.) eight pounds in a hospitalized period of four weeks. Included in the therapy of the latter case were a high caloric diet, antacids and a high vitamin intake. In a follow-up in the four cases who had gained eight to eleven pounds on Norethandrolone, two had retained five pounds three months after discontinuing the drug. A third had returned to his former weight seven months after cessation of the drug.

2. *Weight loss of undetermined origin:*—In five cases where inability to gain weight was of unknown cause the response to the drug appeared to be more uniform and was not attended by factors which seemed to complicate the

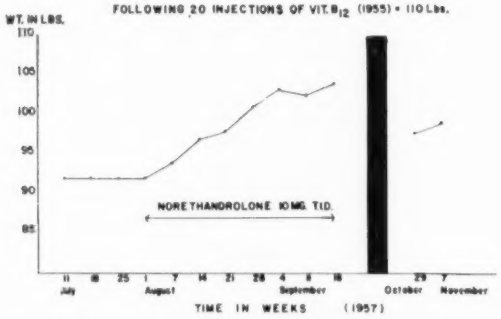

Fig. 1—Case 1, E. B., female, age 48. Weight loss following subtotal gastrectomy. Weight, 1930—133 lbs. Weight at surgery, 1931—103 lbs. Postoperative weight, 1932—98 lbs. Following 20 injections of Vitamin B_{12} (1955)—110 lbs.

first group. There was a weight gain of five pounds in three cases in a four to six-week period of treatment. In the fourth case (G.R.) the weight increases were greater, 11½ pounds in three months' treatment. In the last case where 80 mg. were taken daily for two months, a ten-pound weight increase occurred and a plateau was reached at this point even with continuation of the drug. Increased appetite occurred early in all of the cases only to become less pronounced as the drug was administered.

3. *Weight loss associated with gastrointestinal disease:*—Five cases were treated with the drug. In two cases of ulcerative colitis, Norethandrolone was used concomitantly with a high caloric diet, anticholinergics, vitamins, symptomatic therapy and in one case nonabsorbable sulfas. A weight gain of ten pounds occurred in one with a moderately severe ulcerative involvement of the transverse and descending colon in four weeks of 30 mg. daily and five pounds in

the second case with widespread polypoid involvement of the entire colon. Appetite was increased as well as a sense of well being in both. In one case of a girl of 14 with regional ileitis who had responded well to prednisolone during an acute exacerbation with weight gain, showed no weight gain during one month's administration of the drug, although her appetite became excellent. In the other case of ileitis, where both oral and intramuscular Norethandrolone was given, a weight gain of three pounds with increased appetite occurred in three weeks, with increased sense of well being. Nine months previously when placed on prednisolone an eight-pound increase had occurred in a six weeks' period. A female, aged 33 with a history of repeated small bowel resections for recurrent intestinal obstruction and adhesions with minimal remaining small bowel present, who weighed 98 pounds prior to surgery, gained six pounds in five weeks of 30 mg. daily, but failed to maintain this increase. Two months later

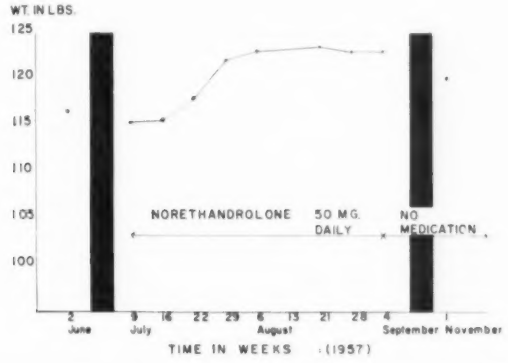

Fig. 2—Case 2, Y. S., female, age 61. Weight gain following subtotal gastrectomy. Weight prior to surgery (1952)—160 lbs. Weight in January 1955—118 lbs.

when her weight was 76 pounds, 60 mg. of the drug daily for one month raised her weight to 78 pounds with marked increase in appetite.

4. Weight loss secondary to malignancy with metastatic spread:—Five cases were included in this group. The first two cases were one of a carcinoma of pancreas with spread to lung, kidney and intestine, and the other of an adenocarcinoma of the breast with metastasis to the liver. Appetite increase was noted in both cases with a two-pound weight increase in one. Both cases expired, one three weeks and the other one week after onset of the administration of the drug. A third case of carcinoma of the stomach with subtotal gastrectomy was given Norethandrolone by intramuscular injection one month following surgery; increase in strength and appetite occurred but no weight increase. The other two cases also responded with increased appetites, one of whom had a marked weight increase.

Side-effects

Side-effects such as edema and disturbances in the menstrual cycle in the females occurred. We noted disturbed menstruation in two females (R.R., R.B.) and a depression of libido and potentia in one male (S.L.). In all these cases a return to normal of these functions took place when the drug was withdrawn. In two cases, edema of the extremities, mild in character, developed (E.B., R.B.) and disappeared at the end of the treatment period. In another case (G.R.), during the early phase of therapy, a right-sided epididymitis intervened of four weeks' duration. The possibility of the latter as being coincidental is strong. No similar side-effect has as yet been previously reported. In one of the gastric resection cases hirsutism developed and disappeared when the drug was stopped. In none of our entire series did we encounter jaundice as a complication as has recently been reported following the use of the drug[3]. Norethandrolone has been shown to produce an azoospermia in approximately ten weeks

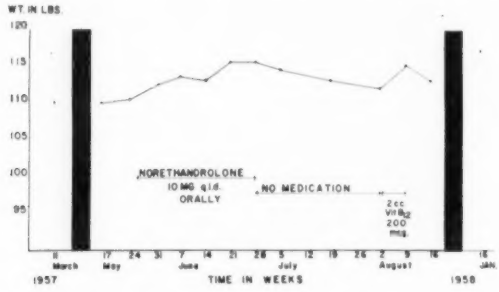

Fig. 3—Case 3, R. R., female, age 42. Weight loss of undetermined origin. January, 1953—120 lbs. January, 1956—90 lbs.

of continuous administration at the dosage level of 40 to 50 mg. a day. Recovery from the azoospermia occurs on the withdrawal of the drug. Norethandrolone has shown itself to be a potent progestin and when taken in adequate dosage will produce effects similar to Norethynodrel[4], the endometropic agent.

When weight loss was associated with symptoms typical of the dumping syndrome it was difficult in a number of cases to continue with the medication unless concomitant relief was obtained. In four cases given the drug intramuscularly at weekly intervals concurrently with oral administration (25 mg.) no increased benefits were noted. In one case in whom Norethandrolone was given in two courses two months apart, the administration of a placebo tablet similar in shape and appearance to the effective drug was not followed by any weight change. In six cases in the postgastrectomy treated group, increases in appetite were definitely present as well as an appreciable sense of well being. This improvement was immediate but of short-term and the effect disappeared

when the distressing symptoms of the "dumping" state reasserted themselves in the symptomatic group.

Case Reports

Case 1, Gastric resection with weight gain:—A white woman (E.B.) aged 48 was first seen 11 July 1957 with complaints relating to a chronic bronchial asthma, migraine headaches, epigastric distress, loose bowels. Her history included a subtotal gastrectomy for duodenal ulcer in September 1931. She also had numbness in her fingers and arthritic manifestations. Her usual weight prior to surgery was 133 pounds. She was begun on the drug on 1 August 1957 (10 mg., three times daily after meals) and was continued on it until 18 September 1957. In this seven-week period she gained 12½ pounds going from 92 to 104½ pounds; seven weeks after the drug was discontinued her weight registered at 99¾ pounds. Three weeks after beginning the drug she began to have increased appetite. The drug was discontinued when nausea and belching associated with

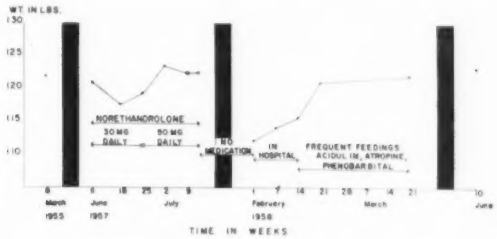

Fig. 4—Case 4, S. L., male, age 43. Weight loss with "dumping syndrome". Weight prior to surgery, 10 August 1953—160 lbs. Weight on first visit, 1 February 1955—120 lbs.

an emotional upset developed. It is of some interest that she stated that in 1955, a weight gain of 14 pounds occurred with a series of Vitamin B_{12} injections.

Case 2, Symptomatic dumping syndrome with weight gain:—A 61-year old white female (Y.S.) was first seen on 1 July 1957. She had symptoms of the dumping syndrome. Her weight, prior to subtotal gastrectomy in 1952 was 160 pounds. Five months prior to the initial interview her weight was 128 pounds. She complained of constant pain in the epigastrium for five years, weakness, feelings of coldness and numbness in the extremities and watery movements after each meal. She was placed on Norethandrolone 50 mg. daily. In the following week she developed increased appetite and felt hungry for the first time in years. She found herself awakening during the middle of the night for food. This continued during the period of administration of the drug. She was also placed on additional therapy which included anticholinergic and antispasmodic drugs, antacids, atropine and small frequent feedings, but continued to have cramps except when she abstained from eating. She reported that she felt stronger. There were no side- or adverse effects of the drug. During the first

week the looseness of the bowels turned to a solid consistency. There was an eight and one-fourth pound weight gain from 9 July to 3 September when the drug was discontinued. Two months after cessation of the drug, five pounds of the increase was still retained while there was no effect on the active symptoms of the dumping syndrome.

Case 3, Weight loss of undetermined origin with response to drug:—A white female aged 42 (R.R.) applied for treatment with an underweight problem. Her weight when first seen on 7 March 1957 was 110 pounds. Her usual weight varied between 115-118 pounds. Her medical complaints were related to a spastic irritable colon. Norethandrolone was administered 24 May (10 mg. t.i.d.) for a period of five weeks and a weight gain of five pounds occurred. Her menstrual flow was disturbed during the therapy and was resumed normally the following month. No drugs were administered until 12 August when a three and one-half pound weight loss occurred. On 16 January 1958 with no further

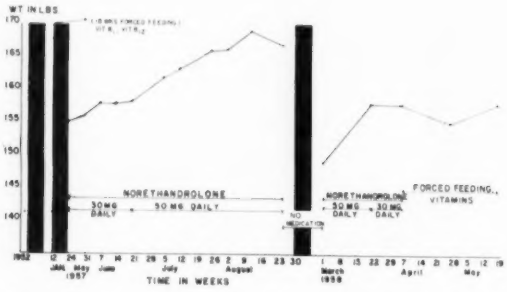

Fig. 5—Case 5, C. R., male, age 29. Weight loss of undetermined origin. Weight, 1941-1945—165-180 lbs.

medication her weight was 117 pounds. On 10 June 1958, her weight was 116 pounds with no medication and she was better in general.

Case 4, Marked weight loss following gastric resection with indifferent response:—A 43-year old male (S.L.) had a history of peptic ulcer since 1945. He had a subtotal gastrectomy performed 10 August 1953 for recurrent gastric ulcer. Prior to the onset of his ulcer symptoms his usual weight was 165 pounds; at the time of surgery his weight was 140 pounds. His weight when first seen by us 1 February 1955 was 121 pounds. He stated that he had the symptoms of the dumping syndrome since one month following surgery (nausea and vomiting, diarrhea and cramps). He gained two pounds over a three-week period when placed on Vitamin B_{12} and Tween 80.

When seen again two and one-half years later his weight was 121 pounds (11 June 1957). He was then placed on Norethandrolone 10 mg., t.i.d. Two weeks later his weight was 119¼ pounds and no change had occurred. He was

then given the drug 10 mg. five times daily, and one week later he weighed 123½ pounds and noted marked improvement in appetite. On 9 July he weighed 122½ pounds and noted a decline in his usually good libido and potentia. He discontinued the drug because of diarrhea, insomnia and increased vomiting and general ill feeling. Six months later his weight had dropped to 112 pounds. Hospitalization and complete study revealed the pertinent findings of a marked abnormality in the glucose tolerance curve and a lack of free acid in a fractional gastric analysis. He was treated with frequent feedings, phenobarbital, acidulin, atropine at meal times and he gained ten pounds in weight. On 21 March 1958 he was asymptomatic and in good health. On 10 June 1958 his weight was 123¾ pounds.

Case 5, Effectiveness of standard treatment of dumping syndrome in weight gain:—A white female aged 37 was first seen 10 January 1958 with a weight of 92 pounds. Six years prior to the first visit she developed a gastric perforation for which gastric resection was performed. Her preoperative weight was 120 pounds. Her previous medications had included antispasmodics, sedatives, acid neutralizers, and tranquilizers. X-rays indicated a normally functioning gastroenterostomy without evidence of obstruction or ulceration. Following two weeks of the drug no weight increase occurred. She was then placed on a program of small frequent feedings, fluid restriction, atropine and amphoteric substances and when seen on 25 April had gained ten pounds and felt improved. She was again placed on Norethandrolone 30 mg. daily in conjunction with the other measures on 23 May when her weight had dropped to 99 pounds. On 20 June she weighed 102 pounds and reported feeling well.

This is an example in which the presently acceptable treatment for the "dumping" syndrome corrected the symptoms and restored weight appreciably and where Norethandrolone was relatively ineffective.

Comment

Information on the activity of Norethandrolone under the usual conditions of practice is not easily available from controlled metabolic balance studies which have served rather to quantitate the anabolic potency of the drug under special conditions. Its performance under clinical circumstances in a uniform series of cases has as yet not been reported. The present findings provide a somewhat broader base upon which to establish relatively more valid impressions.

Comparison between the relative effectiveness of Norethandrolone and other procedures was attempted in the groups under observation. For example, in three patients with gastric resection who had been given Norethandrolone the currently accepted medical regime was followed by appreciable weight increases. In three cases of ulcerative colitis and regional ileitis, steroids used for other acute exacerbations were attended with equal or greater weight gain and

in addition symptomatic relief. While the utility of the hormone for weight gain appears to be present in this relatively small series, its advantage over other therapeutic approaches would not seem to be very great. When previously available measures have proven unsuccessful in weight gain, its use would appear warranted in the individual case.

In one respect all cases reacted uniformly: whatever the degree of weight gain, the immediate increase in appetite and hunger onset as well as a sense of general well being is apparent and at times dramatic in intensity. This did not seem to be invariably sustained. Except for those cases with weight loss of undetermined origin, the drug may be regarded as an adjuvant in treatment, its effectiveness being delimited by the pathologic physiology and disturbed function as a result of the specific disease.

The double blindfold method of evaluating clinical effects of drugs has achieved widespread use. Its importance has become increasingly recognized and any presentation failing to take into account this factor is considered subject to the limitations of these studies. Some misgivings as to the reliability of this method, however, where a subjective element may enter have recently been expressed by Tomenius[5], "The placebo effect is a measure of the suggestive bond between patient and physician. It does not contribute to the statistical evaluation of a drug's activity. Individual observations of patients given various treatments over long periods by the same physician may provide just as exact a method as the double-blind test. Here the suggestive influence is the same throughout and is reduced in importance by the length of the experiment". Again, Sidney Cohen[6] has expressed similar misgivings: "We place as much confidence in serial descriptive reports by skilled observers with minimal emotional investment in drug therapy who are thoroughly acquainted with their patient as in any other measure of drug effect". In two of our cases where a placebo was interspersed for a time during longer periods of observations, no weight change was observed.

The possibility that the effect on the weight gain of the gastrectomized patient is of a nonspecific nature unrelated to the problems inherent to the postoperative state is one to be considered. It is also apparent that other adverse aspects of the dumping syndrome (the immediate and delayed postprandial reactions or the afferent loop syndrome) were not modified or alleviated. It is to be noted in addition that we did not attempt to control or quantitate one variable in these patients, i.e., the dietary intake, since we felt that the medication was to be judged under conditions of clinical practice.

Our experience indicates that in most cases where the drug is tolerated and the dosage by clinical trial is adequate, greater or lesser gains in weight may be expected. Maintenance of the weight levels is difficult when the drug is discontinued. When, however, the drug is repeated at subsequent periods, responses may again be expected. Weight gain was dependent upon the presence

of associated diseases, the previous nutritional state, the age of the patient and his ability to ingest and assimilate increased caloric intake. In the group of cases with weight loss of undetermined origin, the absence of complicating factors made for a more uniform response in weight gain and greater likelihood of permanent gain. Larger doses may at times be necessary when a response is not achieved in the early weeks of administration.

Side-effects, in our experience, while disturbing, proved to be reversible when the drug was discontinued.

Summary and Conclusions

A study of the effect of Norethandrolone to overcome the chronic weight loss following subtotal gastrectomy for ulcer in 10 cases showed weight gains in 80 per cent ranging from 2 to 11 pounds during the administration of the drug.

In 50 per cent of the cases weight gain was not invariably maintained when the drug was discontinued but did not return to former levels. All patients experienced appetite increase and a sense of well being.

The drug had no effect on the adverse symptoms associated with the dumping syndrome. Hormonal side-effects proved reversible. It can be regarded as adjuvant therapy for weight loss, although weight gain in some of these patients occurred with other standard therapies for the syndrome.

In ten cases of inanition secondary to gastrointestinal disease and of unknown origin, more uniform weight gains also occurred during therapy.

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Discussion

Dr. Samuel Weiss (New York, N. Y.):—What is your experience in postmenopausal cases? We had several bad hemorrhages, with dehydration, needing intravenous glucose, transfusions, and curettage.

Dr. Jacob Lichstein (Los Angeles, Calif.):—I can think of two of these patients who were postmenopausal who did not present any complications which Dr. Weiss mentioned such as severe hemorrhages. Neither case tolerated the drug very well at the beginning. There was no severe reaction at all except the one that I mentioned.

One man developed an epididymitis during the course of the administration. I checked the literature but found no other similar cases reported. I felt that this was coincidental.

It is not a drug that can be handled without some close observation of the patient, but it is an interesting drug, and I might say that one of the difficulties is its expense. We have had a sufficient quantity at our disposal so that there is no problem there, but it is a consideration from a practical point of view. I might say it probably has its greatest indication in the immediate postoperative state where weight loss is very great and where the problem of maintaining weight is important.

I haven't reported cases here, but there were some dramatic weight increases following surgery where the drug was given over a short-term period in large doses.

Question:—You refer to weight loss not due to inadequate appetite. The cases appeared to gain weight by increased appetite.

Dr. Lichstein:—We paid no attention to the amount of the intake; in other words, we had no measured amount of calories daily. We made no attempt to see if there was a reversal of any possible nitrogen loss. These matters have been shown in previous cases by careful nitrogen balance studies, in postoperative cases especially. There are two or three references, such as the work of Peden and Maxwell, where, I believe in cases following hysterectomy they used six for controls and studied nitrogen loss, and incidentally reversed by the use of Norethandrolone not only the nitrogen loss but the sodium, potassium and calcium loss, which is the reason why we have to watch for edema. These patients did have increase in appetite and did want to eat more.

SUBMUCOUS LIPOMA OF THE COLON*

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and

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Of all benign growths occurring in the large intestine, lipoma is second in frequency only to adenoma[8,16]. These fatty tumors occur in two forms—submucous, accounting for 90 per cent, and subserous ten per cent. The subserous tumors arise in the appendices epiploicae[6].

Lipomas are of surgical significance when they produce any one of three types of complications, intussusception, obstruction or hemorrhage[10,17]. They are often erroneously diagnosed as carcinoma and treated by unnecessarily radical procedures.

This report is primarily concerned with the submucous form.

History

Bauer[1], in 1757, was the first to describe lipoma of the gastrointestinal tract. Hiller[11], in 1829, reported a series of 23 cases. Since then there have been sporadic reports in the literature. The most recent comprehensive review of the subject was published by D'Alonzo[7] in 1957 and included the description of a case of submucous lipoma of the sigmoid colon in which resection was followed by complete recovery.

Incidence

The frequency of this lesion cannot be estimated accurately because many lipomas cause no symptoms and are discovered only at autopsy or as an incidental finding at operation. Comfort[6], in a series of 3,924 necropsies, found the incidence of submucous lipoma to be 0.5 per cent. Kirschbaum[12] reported an incidence of 0.2 per cent. Long, Dockerty and Waugh[13] found 33 cases of submucous lipoma in 125,000 laparotomies, or an incidence of 0.02 per cent. In a search of the records of Touro Infirmary in New Orleans, La., for a 10-year period, we found only 4 cases.

From the above statistics, the incidence appears to range from 0.02 to 0.5 per cent. With improvement in x-ray technic and more frequent examination

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of the entire colon at laparotomies, the true incidence of lipomas of the large bowel may be found to be higher.

Submucous lipomas have been found in patients between the ages of 16 and 87[17], more than half of the patients being over 39 years of age. The most frequent occurrence is in the fifth and sixth decades. Submucous lipomas are slightly more common in women than in men.

Location

Submucous lipomas are more frequently found in the right half of the colon than in the other segments. In 102 cases Pemberton and McCormack[17] found 29 in the cecum, 21 in the ascending colon, 15 in the transverse colon, 11 in the descending colon, 14 in the sigmoid and 12 in the rectum. D'Alonzo[7] reported that a personal communication from the Armed Forces Institute of Pathology stated that, in their series, 9 lipomas were found in the sigmoid colon and 44 throughout the remainder of the colon. Other collected series[6,11,17,18], while showing various percentages, all indicate that these tumors are more frequently seen in the right colon than elsewhere in the bowel.

Etiology

The etiology of submucous lipomas remains obscure. Several theories have been advanced[3,9,12], none of which satisfactorily explains their origin. This tumor is thought to represent neoplastic proliferation of adipose tissue beginning in a submucous focus. Following the lines of least resistance it grows into the lumen of the bowel and often becomes polypoid. Chronic irritation and inflammation[3] have in the past been considered as possible etiologic factors but are most probably related only to the hypertrophy of the adipose tissue and the trauma to which it is subjected by peristalsis and the fecal stream.

Pathology

Macroscopically, submucous lipomas may be small or they may attain considerable size. As a rule they are well circumscribed and soft in consistency. The mucosa over the small tumors is not involved and has a normal appearance. Over the large tumors, as they grow toward the lumen, the mucosa becomes thin and atrophic. In such instances the characteristic yellow color of the tumor can be seen through the mucosa when the tumor is exposed by a colotomy incision, and in most cases the diagnosis can be made from the gross appearance of the mass. Lipomas may be single or multiple, as was in Case 1. They may be sessile or pedunculated. The large tumors tend to be pushed downward by peristalsis and may develop a long stalk. The mucosa covering a large lipoma may ulcerate and bleed or the tumor may protrude through the mucosa and be

expelled[14]. On cut surface, lipomas may show areas of cystic degeneration and necrosis[2].

Histologically, submucous lipomas of the colon differ in no way from lipomas seen elsewhere in the body and vary from a small collection of fat cells

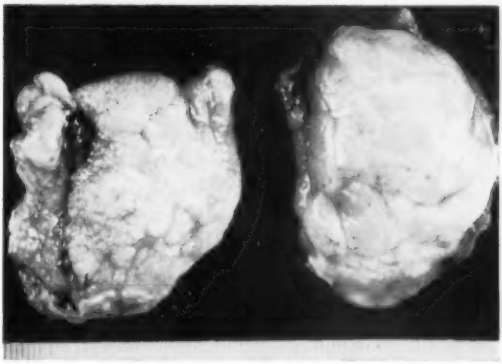

Fig. 1–Large submucous lipoma of colon. The tumor is discrete, soft in consistency and shows no tendency to infiltrate the mucosa or the muscularis.

in the submucosa to a large tumor. As the tumor increases in size the line of demarcation between the submucosal connective tissue and the fat becomes more definite and a thin capsule is formed[6].

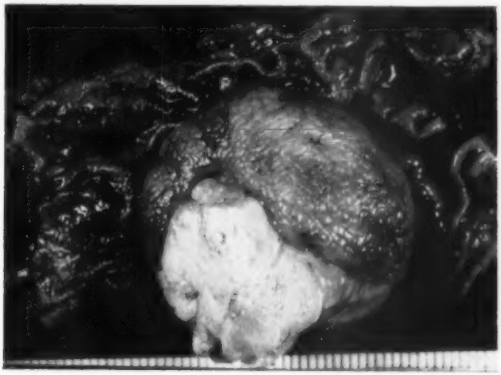

Fig. 2–Large submucous lipoma of the colon which was removed by segmental resection. The tumor is well circumscribed and could easily have been removed by enucleation.

Clinical Manifestations

Generally it may be stated that the symptoms these tumors produce are due to their size, their location and their complications. Small submucous

lipomas of the colon may exist for a long period of time and may be found only incidentally at autopsy. The larger tumors, as they grow toward the lumen of the gut, may interfere with the normal mechanical function of the bowel and, depending upon the segment of the colon in which they are located, produce variable and frequently obscure symptoms for periods of years. All of the large tumors, regardless of location, are apt to undergo ulceration and cause hemorrhage. The atrophic mucosa over the tumor is susceptible to even minor trauma by the fecal stream, and ulceration, bleeding and secondary anemia are not uncommon findings.

The large tumors often depend from long pedicles and, projecting into the lumen of the bowel, act as foreign bodies. The gut, attempting to expel them, may produce such symptoms as pain, diarrhea[4] or intussusception. Intussusception is more common when the tumors are located in the ileocecal region and occurs in 50 per cent of these cases. It occasionally occurs when the lipoma is located in the transverse colon, as in Case 3 of our series.

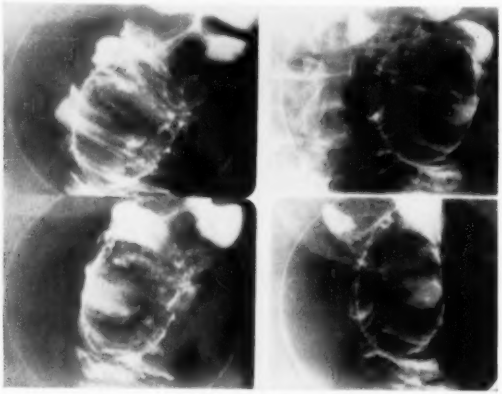

Fig. 3–Case 2. Contrast enema, spot film showing a large submucous lipoma in ascending colon.

When located in the transverse or left colon, these tumors are more apt to give symptoms of a low-grade, chronic obstruction resembling the symptoms of carcinoma such as flatulence, changing bowel habits, melena, cramps, diarrhea or constipation[4].

Diagnosis

Submucous lipomas are not usually detectable by physical examination. Occasionally, however, if large, they may be palpated through the abdominal wall. In none of our 4 cases was the examiner able to palpate a mass.

X-ray studies are the most valuable aids in diagnosis. The criteria for the diagnosis of a benign tumor of the colon by x-ray, as stated by Weber[23], are:

1. Smooth, sharp, filling defects which often may be pushed up and down a few centimeters;
2. Absence of change in the outline of the colon itself;
3. Freedom of the colonic musculature from involvement;
4. Pliancy of the wall of the bowel;
5. Absence, with rare exceptions, of an associated palpable mass.

Fat is more translucent than other tissues so that a lipoma may appear as a darker mass on the film[19].

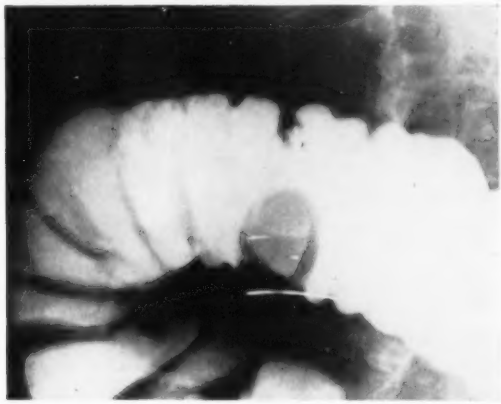

Fig. 4—Case 3. Barium enema showing a large filling defect in transverse colon.

Barium air double contrast enema is also helpful in the diagnosis of such lesions.

Preoperatively it may be impossible to make a differential diagnosis between a benign and a malignant growth, and only an exploratory laparotomy and colotomy will reveal the true nature of the tumor.

Therapy

Many procedures have been reported as treatment for these tumors, ranging from cautery removal, simple enucleation and pedicle ligation to segmental resection, hemicolectomy and abdominal perineal resection[6,7,17]. Radical procedures are rarely necessary and only tend to increase the morbidity and mortality. Malignant changes in these tumors are unreported.

A colotomy incision reveals a circumscribed, encapsulated tumor, sessile or pedunculated, with uninvolved overlying mucosa, which is usually thin over the large tumors and through which the characteristic yellowish color of the tumor may be seen. The musculature shows no evidence of infiltration. If the tumor is sessile, it can easily be shelled out through an incision in the overlying mucosa and the mucosa closed over the defect with a number of interrupted chromic 00 sutures. The pedicle, if the tumor has one, can be transfixed and ligated flush with the mucosal wall. Frozen sections should be done to verify the clin-

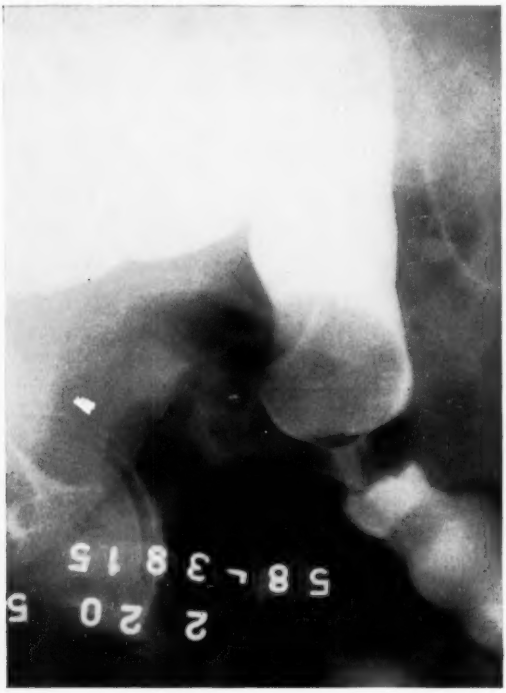

Fig. 5—Case 4. Barium enema showing a large sharply defined defect in sigmoid colon.

ical diagnosis. Because these tumors are often multiple, as in our Case 1, a search of the entire colon should be made.

Case Reports

Brief summaries of the case histories of the 4 patients who were treated for submucous lipomas of the colon at Touro Infirmary, New Orleans, in the past 10 years illustrate the foregoing points:

Case 1:—A 69-year old white female was admitted to Touro Infirmary on 13 May 1954, with a chief complaint of cramping abdominal pain of one to one and a half months' duration. The pain was localized in the lower abdomen and followed meals, though at no specific time interval. On the day prior to admission she first noted bright blood intermixed with stools. The abdominal pain had become more intense and cramping in nature.

Past history revealed that the patient had had a hemorrhoidectomy and a rectal polypectomy 8 years prior to admission and a cholecystectomy and appendectomy 6 years later. The patient had been treated for arteriosclerotic heart disease in the past.

Physical examination revealed a well developed, well nourished, elderly, white female in no acute distress. Blood pressure was 120/70 and pulse 86/min. Examination of the eyes, ears, nose and throat was negative. The lungs were clear to auscultation. The heart was not clinically enlarged and the rhythm was regular. The abdomen was obese and showed scars of previous operations. The liver, spleen and kidneys were not palpable. No masses were palpable. There was minimal tenderness on the right side but no rigidity was noted.

Laboratory examination showed a hemoglobin of 10.6 gm., leucocytes 10,600 with 82 per cent neutrophiles and 17 per cent lymphocytes. Urinalysis gave findings within normal limits. Blood glucose was 105 mg. per cent and N.P.N. 34 mg. per cent.

Barium enema on the day following admission revealed an obstruction to the flow of barium in the region of the proximal transverse colon. A large filling defect was noted in this area which proved on further examination to be a polypoid lesion approximately 5 cm. in diameter on the medial aspect of the ascending colon just below the hepatic flexure. The polyp and a short segment of ascending colon were noted to be transiently intussuscepted into the transverse colon. The intussusception was reduced by the introduction of air, at which time the polyp was well outlined.

On 25 May 1954, a large sessile lipoma of the ascending colon was excised. Exploration of the ileocecal valve revealed another submucosal lipoma which was also excised. Grossly, the lipomas were covered by colonic mucosa, which, in the larger specimen, showed areas of ulceration. Histologically, the tumors were composed of well differentiated adipose tissue. The larger tumor showed acute and chronic inflammatory changes in the overlying mucosa.

Case 2:—A 49-year old white male was admitted to Touro Infirmary 26 November 1957, with a chief complaint of pain in the right lower quadrant of two months' duration. The pain was dull and intermittent and was described by the patient as more of a discomfort than an actual pain. During this two-month interval he had lost no weight and had had no change in bowel habits. There had been no melena nor bright red rectal bleeding.

System review and past medical history were not remarkable.

Physical examination showed the blood pressure to be 135/70, the pulse 80/min., respirations 18/min. and temperature 98.6°. Examination of the eyes, ears, nose and throat was negative. The lungs were clear to auscultation and percussion. The heart was normal. The liver and spleen were not palpable. In the abdomen no masses were palpated and no tenderness was noted.

The hemoglobin was 11.4 gm., hematocrit 38, leucocytes 9,600 with 52 per cent neutrophiles, 3 per cent eosinophiles and 45 per cent lymphocytes. Urinalysis and routine blood chemistry determinations gave results within normal limits. A barium enema revealed no obstructive lesion within the large bowel. Postevacuation studies, including compression spot films, showed a sharply defined, ovoid tumor in the ascending colon distal to the ileocecal valve. There was no localized tenderness and the bowel was freely movable.

On 27 November 1957, a submucosal lipoma was excised from the cecum. The tumor measured 5.5 x 4.5 x 2 cm. and was a flattened, well circumscribed, mass of coarsely lobulated fatty tissue. Histologically, the tumor was composed of well differentiated adipose tissue.

Case 3:—A 70-year old white female was admitted to Touro Infirmary 4 March 1958, for operation following discovery by barium enema of a polyp in the sigmoid colon.

Physical examination gave essentially normal findings. There was no abdominal tenderness nor could any mass be palpated.

Routine laboratory work showed the hemoglobin to be 12.9 gm., hematocrit 40, leucocytes 5,900 with 60 per cent neutrophiles and 36 per cent lymphocytes. Urinalysis as well as blood glucose and N.P.N. determinations gave results within normal limits.

On 5 March 1958, a pedunculated lipoma was removed from the sigmoid colon by pedicle ligation. Grossly, the tumor measured 2.5 x 2.5 cm. and was attached to the bowel by a pedicle measuring 0.3 cm. The overlying bowel mucosa was intact. Histologically, the tumor was composed of well differentiated adipose tissue.

Case 4:—A 70-year old white female was first seen by her physician in the latter part of October, 1955 complaining of epigastric and left lower quadrant pain of five to six years' duration. At times the pain was burning in nature and at other times cramping. On occasion nausea and vomiting had been associated with the pain. There was no history of melena or bright red rectal bleeding. A barium enema revealed a polypoid lesion of the transverse colon. The patient was hospitalized for operation 21 November 1955.

Past history showed that the patient had had a cholecystectomy and a thyroidectomy.

Physical examination revealed a well developed, well nourished, elderly white female. The blood pressure was 160/110 and the pulse regular at 90/min. Examination of the eyes, ears, nose and throat was negative. The heart and lungs were normal to physical examination. The liver and spleen were not palpable. There was some tenderness on palpation over the epigastrium and minimal tenderness in the left lower quadrant. No rebound was noted and there were no palpable masses.

Laboratory work revealed a hemoglobin of 14.4 gm., hematocrit 45, leucocytes 6,200 with 60 per cent neutrophiles and 32 per cent lymphocytes. Urinalysis gave normal results as did blood glucose and N.P.N. determinations.

On 22 November 1955, two submucosal lipomas were excised from the transverse colon. The softness of the tumors prohibited adequate localization, requiring direct proctoscopic visualization. Grossly, the tumors were characteristic lipomas with intact overlying mucosa. Histologically, they were composed of well differentiated adipose tissue.

Comment

Lipomas are most frequently found in subjects of middle and advanced age and, when they produce symptoms, are clinically indistinguishable from carcinoma of the colon. The roentgenologist can be of considerable help in demonstrating the presence of a polypoid tumor of the colon, often showing ulceration of its surface or causing partial obstruction. Excision biopsy, however, is the only means of differentiating between these fatty polyps and carcinomas and surgical exploration should not be delayed. With the knowledge that such tumors exist, the diagnosis can be made in most instances on the basis of the gross findings at operation. Absence of infiltration of the serosa and musculature of the gut and absence of glandular involvement indicate a benign lesion, and a colotomy incision should be performed. Because thorough preoperative preparation of the bowel is now done routinely, there is little danger of contamination. Through the colotomy incision the surgeon can evaluate the nature of the tumor. A polypoid or sessile tumor with a yellowish color and uninvolved mucosal covering is suggestive of a submucous lipoma. Local excision and frozen section will verify the diagnosis and obviate a radical procedure.

Summary

1. Four cases of submucous lipomas of the colon have been presented, one found in the cecum, one in the ascending colon, one in the proximal transverse colon and one in the sigmoid.

2. Lipomas occur in two forms, submucous (90 per cent) and subserous (10 per cent). The submucous variety may be sessile or pedunculated.

3. Submucous lipomas are more common in middle and advanced age.

4. They occur in the right colon more frequently than elsewhere in the intestines.

5. The symptoms they produce are due to their size, location and their complications which may include intussusception, obstruction, ulceration and bleeding. In rare instances they may be expelled from the colon.

6. Through a colotomy incision, and with the knowledge that these tumors exist, the surgeon can usually make the diagnosis on the basis of the gross appearance of the tumor.

7. The diagnosis should be verified by frozen section.

8. Malignant changes in these tumors are unreported and radical procedures are seldom necessary.

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Discussion

Dr. M. L. Michel (New Orleans, La.):–This has been an excellent and complete presentation by Dr. Kaplan. These cases were handled in the ideal way, i.e. by colotomy and excision of the lesion rather than by colectomy.

In the occasional case, the lipoma may be so large and necrotic changes may have occurred so that resection is necessary. Such a case recently occurred on the Tulane Service at Charity Hospital:

A white female, age 35, had diarrhea for nine days previous to admission–six days of watery diarrhea and three days of bloody diarrhea–accompanied by cramping abdominal pains of increasing severity. There had been no previous symptoms.

The general physical examination was essentially negative. On rectal examination, a mass 5 to 6 cm. from the anus was felt, filling the entire ampulla of the rectum. Proctoscopic examination revealed a red, edematous mass that was slightly movable. Biopsy of this mass showed nonspecific acute inflammatory tissue. No specific diagnosis could be made. Barium enema was not done because of the degree of obstruction.

After antibiotic bowel preparation, which was possible because the patient was not completely obstructed, laparotomy revealed a secondary intussusception due to an intraluminal tumor of the sigmoid colon.

There was necrosis of the colon and it was necessary to do a colectomy rather than risk a colotomy.

This case illustrates the importance of early diagnosis. If the patient had been seen earlier in the disease, colectomy would not have been necessary.

I agree with Dr. Kaplan that there is rarely an indication for colectomy, particularly if the diagnosis can be made before necrotic changes have occurred. Malignant changes in these lesions have not been reported.

We believe that all patients past 40 should have a barium enema as part of a complete diagnostic survey, even if they have no bowel symptoms. It is entirely possible that the radiologists will diagnose asymptomatic lipomas of the colon in the future.

What should we do with these? In my opinion they should be removed for two reasons; first, because of the danger of intussusception and other complications; and, secondly, although we can be reasonably correct in the x-ray diagnosis, the x-ray defect may be due to carcinoma of the colon, which is much more common than lipoma.

Clinicopathological Conference

from the Touro Infirmary, New Orleans, La.

*Dr. Ambrose Hertzog**:—We have had cases of Nieman-Pick's disease, Osler-Rendu-Weber's disease, and bilateral renal vein thrombosis but the clinicians always make the diagnosis. On this occasion, Dr. John M. McMahon, a former staff member of Touro but now of Birmingham, is presenting this case which Dr. Gordon McHardy will discuss.

PROTOCOL

Dr. John M. McMahon†:—This patient is a 24-year old white male who was first seen by his physician on 18 June 1955 at which time an emergency appendectomy was performed for acute appendicitis. Convalescence was satisfactory. He received intravenous fluids and several parenteral injections postoperatively, but no blood transfusions. He returned on 10 August 1955 with the history of onset two weeks previously of anorexia, nausea, malaise, dark urine, and clinical jaundice. He worked during the first week of illness but rested the second week with improvement in his anorexia, nausea and jaundice.

Examination revealed a well developed, well nourished white male with marked scleral icterus. The liver edge was three inches below the costal margin and a recent right rectus appendectomy scar was well healed. Hospitalization was refused for economic reasons. A clinical diagnosis of serum hepatitis was suspected. The patient was sent home on a program of bed rest, liver diet and supplementary vitamins.

He was next seen on 16 January 1956 reporting cough and hemoptysis, ankle edema and dyspnea for the past three months. On examination he was obviously short of breath at rest. The blood pressure varied from 160/120 to 180/130. Examination of the occular fundi revealed narrowing of the arterioles. There was dullness over the lower half of both lungs to percussion and breath sounds were distant. A blow was heard at the apex of the heart which was felt to be diastolic. A thrill was absent. An inconstant pleuropericardial murmur was also noted. The liver filled up the right upper quadrant of the abdomen and extended into the left upper quadrant. There was two plus edema of the legs. X-ray of the chest confirmed the presence of massive bilateral pleural effusion. He was hospitalized at Birmingham Baptist Hospital from 19 to 28 January 1956 with a diagnosis of heart failure, etiology undetermined. The blood pressure was noted to fluctuate markedly while in the hospital. He responded with adequate diuresis to a salt-free diet, Digitoxin for digitalization and the use of mercurial diuretics.

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*Pathologist, Touro Infirmary.

†Assistant Clinical Professor of Medicine, University of Alabama College of Medicine.

During February 1956 repeated office visits were necessary because of the reaccumulation of pleural fluid at both bases. The Congo Red test was negative while the blood pressure continued to vary from 100/70 to 120/100. In late February 1956 he was referred to Dr. R. W. Bing at the University of Alabama Medical Center. Dr. Bing's conclusion: "We do not believe that the patient has primary heart disease." He continued to be observed during the first half of 1956 at which time numerous studies were done including an *L.E.* preparation and guinea pig innoculation of pleural fluid, all with negative results.

With gradual improvement his blood pressure remained in the normal range, and his heart failure first became more readily manageable, then disappeared completely. The liver, however, remained greatly enlarged, at least five fingers below the costal margin.

When next seen in April 1957, he was still short of breath. His legs had become swollen, the abdomen markedly enlarged while he continued to be incapacitated during the previous winter. The blood pressure at this time was 130/96, heart tones normal and fluid absent from the lungs. There was massive enlargement of the liver with about a one plus pitting edema of the skin in the abdominal wall. At this time he was again hospitalized at Birmingham Baptist Hospital from 2 to 10 May 1957. Liver profile was summarized as follows: Marked BSP retention (34 per cent after 45 minutes), diminished prothrombin activity (56 per cent), and positive van den Bergh indirect-slight. Electrophoretic pattern showed moderate hypergammaglobulinemia. Liver biopsy with the Vim needle was reported as normal. During the summer of 1957 the fluid in the abdomen could not be controlled by dietary or medical means. Paracentesis was necessary on two occasions. Third hospitalization in August 1957 with essentially the same findings. Liver profile unchanged except for 16 per cent BSP retention and alkaline phosphatase of 13.5. Chest x-ray was reported as normal. Blood pressure was within normal range on repeated observations. There was no further evidence of a heart murmur. On 29 July 1957 an abdominal exploration was performed.

*Dr. Gordon McHardy**:—Since this is a "foreign" case, I sought out assistance from Europe; I have with me today Dr. Geoffrey Watkinson of Leeds, England. Wherever I leave off, he can take over. If I have not isolated something bizarre enough, perhaps he can develop some entity from across the sea to cloud the issue further. All of you have probably reviewed the protocol. This patient, a 24-year old man, and I bring your attention to his age, white, male, was first seen on 18 June 1955, at which time an emergency appendectomy was performed. I am presuming it was an acute appendix, since it is stated to be acute and not merely appendicitis. Thereby is eliminated functioning carcinoidosis on the basis of carcinoid of the appendix. His convalescence was satis-

*Associate Professor of Medicine, Louisiana State University School of Medicine.

factory which gives us the opportunity of eliminating the possibility of his having portal pyelphlebitis or venous occlusive disease in the postoperative period. Perhaps that simplifies things a degree. He received intravenous fluids and parenteral injections. Dr. McMahon tells me that he was transfused; this is a protocol error. He was next seen on 10 August (7 weeks later) jaundiced: the interval, therefore, is rather perfect for the diagnosis that was concluded, that is, that he probably had a serum hepatitis. His symptomatology, anorexia, nausea, jaundice, and other factors, seems to support the diagnosis at this time. The patient was sent home and apparently responded to a program of bed rest, liver diet, and supplementary vitamins. Obviously, the conclusion at that point was serum hepatitis. It is stated that his jaundice had cleared.

He is next seen some six months after surgery, on 16 January 1956. We presume his jaundice was cleared, though not mentioned; this we conclude supports the probability of a serum hepatitis. On this occasion, he had developed a cough with hemoptysis, and he had, as becomes obvious from the protocol, congestive failure with dyspnea and ankle edema. So we assume that this was conclusively hemoptysis and not hematemesis. We are not, therefore, dealing with acute early bleeding esophageal varices. His vascular difficulties apparently were associated or precipitated by hypertension with a reading as high as 180/130. While we suspect from the history and the findings that he had congestive failure, we do not have the etiological background for the hypertension. He is recorded as having a bilateral pleural effusion. A diastolic apical murmur is described suggesting that this was organic and not merely due to cardiac dilatation. The protocol records a pleuropericardial murmur; I presume this is an error and that a rub was present. He, therefore, had some degree of pleuropericarditis at this time. The liver filled his entire right abdomen and since he has been in congestive failure for three months, perhaps his liver enlargement was purely the result of congestion; i.e. a "cardiac cirrhosis".

Possibilities that enter my mind at this time are that this man may have had an aldosteroma or collagen disease. Aldosteroma seems to be favored by the fact that he now had hypertension. He was managed as a cardiac with sodium restriction and that could bring about a response both in his cardiac status and in his hypertension should aldosteronism exist. The pleuropericarditis could be a part of this disease or a collagen factor. The fact that this heart disease was not refractory seems to correspond to aldosteronism. I am told that all the laboratory procedures were negative other than those that are indicated as positive. I wonder if he had a hypokalemic acidosis to go along with aldosteronism? He was managed, as we see, as a cardiac, diagnosed as "heart failure", and along went the situation.

In February 1956, a Congo Red Test was done and we presume that thereby amyloid disease of the liver was eliminated. You will notice at this time that

his blood pressure approached normal. He had a high diastolic on one reading, but his blood pressure was recorded as low as 100/70. We have the help of an excellent consultant, Dr. R. W. Bing, who states "we do not believe that the patient has primary heart disease." So we presume that heart disease is perhaps out of the picture. Then he had a series of studies; an *L.E.* preparation which was normal, and a guinea pig disproved tuberculosis. All other laboratory procedures are verified as normal by Dr. McMahon. With renal function studies normal, the nephrotic stage of nephritis is rejected.

He improved gradually. His blood pressure remained normal. His cardiovascular state was readily manageable and improved yet his hepatomegaly persisted.

Fig. 1

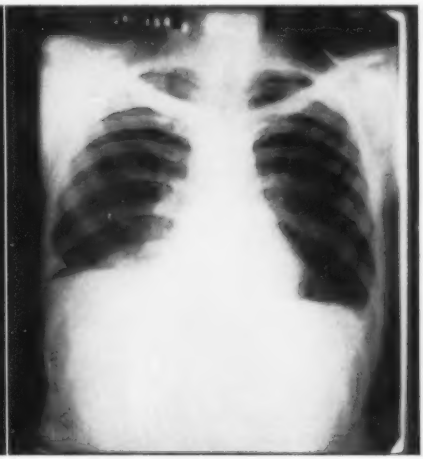

Fig. 2

He was next seen in April 1957. Time is passing, and I believe that time rules out venous occlusive disease since most of those patients expire within six months. The liver is usually atrophic within six months. Now he had massive liver enlargement accompanied by ascites, and a disturbance in his prothrombin time with an indirect van den Bergh elevation. His electrophoretic pattern was that of a gamma hyperglobulinemia, offering conclusive evidence of hepatocellular damage. Though the liver biopsy was reported as normal, I wonder whether it was normal or just reported as normal?

Dr. McMahon:—In my opinion, there may have been some changes.

Dr. McHardy:—That's rather evasive. It perhaps changes the picture to some degree. Regardless, this individual developed ascites that required para-

centesis. He was managed medically but persisted refractory in relation to the ascites.

On re-hospitalization August 1957, the alkaline phosphatase is high (13.5). There is no further mention of bilirubins, so I presume he is not jaundiced. His BSP retention was 16 per cent. His chest films are negative. His heart is radiologically normal in size. I presume his electrocardiogram was normal—is that correct?

Dr. McMahon:—Yes.

Dr. McHardy:—It appears that everything was going along nicely, that is, towards a surgical exploration. Two years and one month after the initial epi-

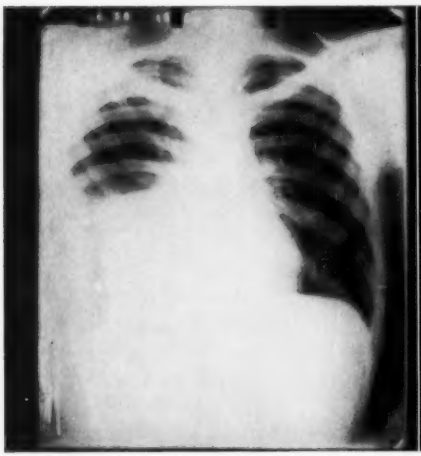

Fig. 3

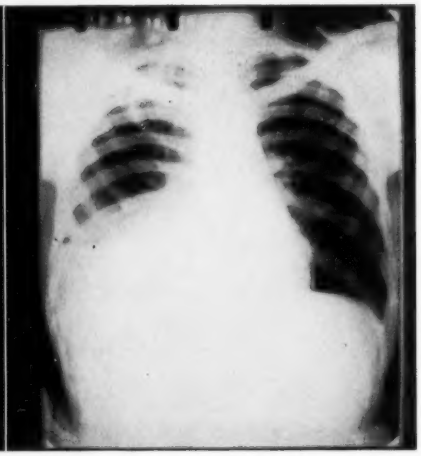

Fig. 4

sode of jaundice we have a patient ready for surgery. Is the surgery, therefore, diagnostic, therapeutic, or just what? This is an extremely provocative case at this point. I think we should, therefore, look into the differential diagnoses.

I am inclined to favor an aldosteroma because I feel the surgical desire was both diagnostic and therapeutic, with the hope of achieving a curative procedure. It would fit the hypertension, the cardiac element, the responsiveness during periods when the patient was on sodium restriction. So that stands as a possibility.

Cardiac cirrhosis could explain the hepatic enlargement but we are told that this is not primary cardiac disease. The long-standing failure that this man obviously had could, however, cause fibrous hepatic changes which might have been equivocal to the pathologist.

A pigment cirrhosis, i.e. hemochromatosis, seems unlikely. This man does not have diabetes or any of the other factors. His biopsy should have been positive for hemosiderin deposition. A lupoid hepatitis?—his *L.E.* preparations were reported as negative. Beyond that, the entire picture could go along with such a diganosis. The biopsy here, however, should show some fibrosis, and nodular changes, with cellular infiltration. If amyloidosis, the biopsy and Congo Red test should have been positive. This doesn't fit Dubin-Johnson or Gilbert's disease in his long history and severity of illness. I think we can eliminate the venous occlusive diseases—portal pyelophlebitis and infarction. Such things as *periarteritis nodosa* should have been excluded by the background at this time.

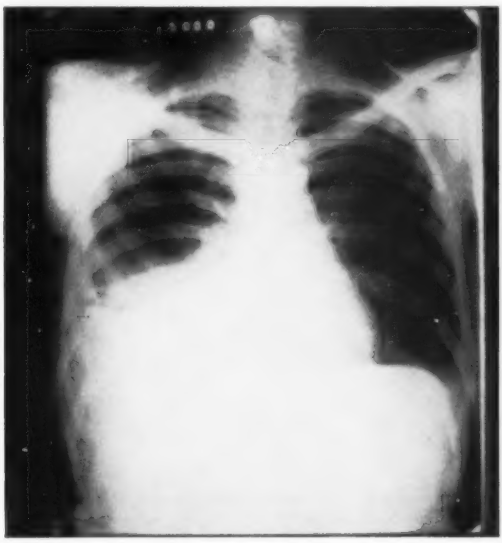

Fig. 5

Since I had this protocol a little bit ahead of time, I looked up all the various possibilities. I sought help from Dr. Randolph Rovelstad[1] who recently reviewed their cases of ascites at the Mayo Clinic—some 116 cases, 81 per cent of these being due to either carcinoma or cirrhosis, and the remaining 22 patients falling into these possibilities: hemochromatosis, chronic constrictive pericarditis, cardiac failure, traumatic arteriovenous fistula, chronic myelogenous leukemia, cirrhosis with hepatoma, bile peritonitis, chronic pancreatitis, portal thrombosis, agnogenic myeloid metaplasia, chronic glomerulonephritis with uremia, so-called nephrosis and mesenteric venous thrombosis. I hope that I haven't omitted any possibilities.

Now, again, why would one consider surgery? As stated, it probably is either diagnostic or therapeutic in this patient's extreme illness. Diagnostically, surgery might expose an aldosteroma, or a malignancy while permitting a necessary biopsy. If *periarteritis nodosa* were under consideration, an abdominal exploratory is contraindicated. Therapeutically, abdominal exploration with a shunt procedure might be indicated but obviously, that was not the case anywhere in the history. Again, for therapeutic reasons, surgery would allow removing an aldosteroma or a carcinoid; this patient did not, however, have the picture of a functioning carcinoidosis.

Fig. 6

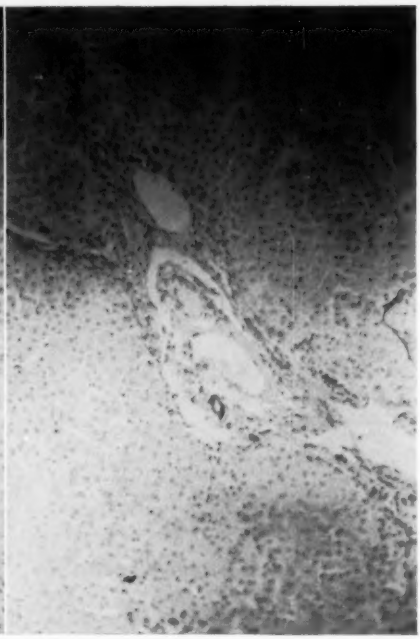

Fig. 7

I have gone through all the reasonable possibilities associated with ascites, those related to jaundice, and those relating to cardiovascular disease. I would like to conclude by thinking that this patient had a serum hepatitis initially. Then, that for some reason, he developed a lesion that caused congestive heart failure. My opinion leans toward either an aldosteroma or the secondary possibility, of constrictive pericarditis, the latter quite unlikely.

Dr. Hertzog:—Before we ask Dr. Watkinson to speak, we will get Dr. Payzant to show the x-rays.

Dr. Arthur R. Payzant:—We have about five x-rays of the chest taken over a six-month period. These show bilateral pleural effusion. The first film shows a fairly definite bilateral accumulation of fluid (Fig. 1). There is a small calcification—probably tuberculous in the left upper lobe, but no evidence of an active pulmonary lesion. The next film was made after a considerable amount of the fluid had been evacuated and revealed that the heart is of normal size (Fig. 2). The vessel markings at this time appear to be of average caliber, and do not suggest congestive failure. In the previous films there is so much fluid that evaluation of the vascular pattern is somewhat difficult. Again there was a reaccumulation of fluid and in the next particular film (Fig. 3) there is an air fluid level which is the stomach. As you will see, this lies against the diaphragm and we wonder whether possibly there might be some lesion above the stomach interposed between the stomach and diaphragm. It could possibly be produced by the spleen which sometimes slides up and over above the stomach. The other two films show essentially the same findings, recurrent effusion more on the right side (Figs. 4 and 5). Some air shadows that are present in several of the films apparently are, I suppose, after thoracentesis.

Dr. Hertzog:—The x-rays don't add very much to what was stated in the protocol. Dr. McHardy has mentioned that we are honored to have a guest from the University of Leeds, England, Dr. Geoffrey Watkinson.

Dr. Geoffrey Watkinson:—I am honored to be here today. After reading this protocol my first inclination was to take a plane out of town. I feel rather like an indifferent batsman who is rather low in the list of batsmen but is called on to make quite a show. On reading through the protocol the first thing that came to my mind was the possibility of venous-occlusive disease. This might have occurred initially postoperatively, first involving the mesenteric veins. Later it could have spread to the inferior *vena cava*, and that might have induced the hepatic part of the syndrome. It might have embolized proximally and induced multiple pulmonary emboli which would have caused the hemoptysis and the pleurisy. It might have spread distally to involve the origin of the renal veins and that might have been the basis for the hypertension, which we know may occur with renal vein occlusion secondary to *vena caval* obstruction. This might not be just a postoperative thrombosis. It might result from some sort of pressure on the inferior *vena cava*, and I wondered if some kind of intrahepatic metastasis might be causing this *caval* pressure.

I have seen two examples in adults of congenital anomalies which produced a picture of this type. I've seen a cavernous replacement of the inferior *vena cava* where symptoms were delayed until the thirties and I've also seen a young man who had a persistent eustachian valve above the origin of the hepatic vein. I wondered if any studies were done to exclude obstruction of the *cava*, such as femoral venography or catheter studies. The next thing that came to mind was the possibility of an aldosterone secreting tumor. This might explain the

heart failure in the absence of obvious heart disease, and it might explain the diagnostic and therapeutic need for a laparotomy. But it would not explain the coincident jaundice. You might get out of that quite easily by saying that this was a serum hepatitis. The incubation period is just correct and there is the history of a possible infective factor. In my experience hypertension is usually more severe and more persistent, and usually persists until the tumor is excised. Have we any studies on the electrolytes? Was there any hypochloremia at any stage? Were there any air studies done?

Dr. McMahon:—No.

Dr. Watkinson:—Very often the Conn syndrome is mimicked by a salt losing nephritis in which one gets a selective potassium loss and I assume from the protocol that renal function tests were normal. Were they?

Dr. McMahon:—Yes.

Dr. Watkinson:—And there was never albuminuria?

Dr. McMahon:—No.

Dr. Watkinson:—I then considered the possibility of a secreting carcinoid metastasis. This would explain the heart failure. It would explain the transient murmur that was noted perhaps, but it certainly is not the typical murmur of a pulmonary valve lesion; but I would have expected a much more progressive course and expected a history of flushing which does not seem to have been present in this case. Liver disease, i.e. hepatic cirrhosis, seems a very distinct possibility and I too would like a more precise opinion on the hepatic biopsy findings. Very often in hepatic cirrhosis the changes are minimal. I too considered the possibility of amyloid, but would have expected in such a severe case to find evidence for it in the liver biopsy. Disseminated collagen disease; this would have explained the abdominal symptoms, the hepatic involvement by way of a lupoid hepatitis, the heart failure, the hyperglobulinemia, but is not suggested by the absence of *L.E.* cells in the blood, the normal liver histology and the absence of renal involvement which one would have expected to have occurred by this stage. I considered the possibility of *periarteritis nodosa.* This frequently presents as an acute abdominal condition. It might explain hemoptysis, heart failure, renal involvement. It might even cause pleurisy and changes in the plasma proteins. In this condition, however, the hypertension is usually progressive and persistent, and there is usually renal involvement. So that too, is not suggested by this picture. I considered the possibility of some occlusive disease affecting the inferior *vena cava,* either a postoperative phenomena, pressure phenomena, or some kind of congenital anomaly presenting in this way. With Dr. McHardy, I would consider the combined diagnosis of serum hepatitis and secreting aldosterone tumor.

Dr. Hertzog:—Thank you, Dr. Watkinson. I was enthused with that diagnosis of aldosteroma or aldosteronism. The adrenal cortex may give rise to

hyperplasia or functional tumors which may be manifested by a Cushing-like syndrome where you have an excess corticosteroid excretion, or it may manifest itself by excessive 17 keto-steroids and virulism. The third type is aldosteronism where one has a disturbance of the electrolytes. Now are there any questions you would like to ask?

Dr. Sam Threefoot:—I assume that this was not in the protocol—but was venous pressure taken in arms and legs or both?

Dr. McMahon:—I don't believe this was done.

Dr. Hertzog:—Dr. Threefoot has polled the Tulane Medical students.

Dr. Threefoot:—The students studied a long list of possible diagnoses. Two thought this was cirrhosis secondary to the hepatitis, one chose amyloidosis as his diagnosis. Three suggested the possibility of carcinoid. One of these three thought that this was a Chiari's syndrome secondary to a carcinoid. One selected the Dubin-Johnson syndrome and another a liver abscess. We have quite an assortment of diagnoses from the students.

Dr. Hertzog:—We'd like to have some diagnoses from the floor. Dr. William Davis cannot come over without giving us a diagnosis:

Dr. William D. Davis, Jr.:—I'd like to see the biopsy. I can't even make a diagnosis in the case of liver disease without seeing the biopsy. It is very easy though for a biopsy to be reported as negative sometime, and to have some telltale evidence in it. Particularly, in postnecrotic cirrhosis, one or two large regenerative nodules may expose the parenchyma to look perfectly normal. Unless one is careful to look for eccentric central veins and minor fibrillary strands of fibrosis, the diagnosis could be missed completely. There are lesions like histoplasmosis which occur in the liver occasionally and can be overlooked unless a careful study of the sinusoids for macrophages is done. I do not actually know what the diagnosis is in this instance. I am intrigued by aldosteroma and I am most interested to see its verification. I also tend to be in agreement with the possibility of venous-occlusive disease; in our experience we had one patient with Chiari's syndrome who recovered and as far as we can tell, it was the result of anticoagulants administered at the height of his difficulty. I wonder if an occasional patient gets a spontaneous semiremission. Certainly, this might have occurred in this instance. Perhaps the entire problem can be explained on the basis of simple homologous serum jaundice with a subsequent postnecrotic cirrhosis. It is difficult to explain the hypertension on that basis unless this patient was so sick that he just willed the hypertension for himself. His circulatory disturbance might have been so severe as a result of fluid retention that he developed hypertension; I would like to have that possibility as one of the considerations.

Dr. Hertzog:—Any questions or comments? I'll ask Dr. McMahon to report on the findings.

Dr. McMahon:—I appreciate being asked to come down and present this case. I'd like to say that this patient lived outside of Jefferson County and the set-up in Alabama is such that only patients who reside in the County can be hospitalized on the charity service at University Hospital in Birmingham. Consequently, we were handicapped in regard to the studies we could do until he was finally taken as a charity patient at Birmingham Baptist Hospital about a year and a half after the onset of his illness. I think the discussers here have been most astute. Because of the unusual aspects of the case, surgery was recommended as a diagnostic procedure and the patient was explored by Dr. Herbert Carmichael of the surgical staff of Baptist Hospital. The entire exploration of the abdomen was negative with the exception of the liver. Grossly a cirrhosis was found. The liver was greatly enlarged and diffuse nodular changes were found all over the liver with nodules of approximately ¼ to 1 cm. in diameter. There was no evidence of a tumor in the adrenal glands or evidence of any other pathology. I'd like to say something more about this after you discuss the slides.

Dr. Hertzog:—Here is a biopsy taken with a scalpel at the time of operation (Figs. 6 and 7). You will notice that most of the abnormality and histolgic aberration is the destruction of the lobular architecture. I saw the needle biopsy of the liver and don't believe I could add to that stated on the protocol; I don't consider it diagnostic, but Dr. Davis can look at it later. This type of section in a needle biopsy is not going to show very much. A diagnosis of cirrhosis of the liver is largely made on the over all architectural pattern with a disorder regeneration of the lobules. This is not a very coarse cirrhosis. This may represent one of those areas of regeneration that was noted. The next slide doesn't show very much either. There is a portal space with some fibrosis of the portal triad, but the hepatic cells themselves look fairly normal. I think a diagnosis of postnecrotic cirrhosis is justified on the basis of the gross findings and the low power photomicrograph.

Dr. McMahon:—I think we can conclude that this is a case of postnecrotic cirrhosis that had been followed from the original episode of serum hepatitis. Both discussers agreed with us that serum hepatitis was present when the patient was originally seen about six weeks following surgery. Now the peculiar aspect of the problem which everyone has mentioned is why did he develop hypertension and heart failure—both being reversible. This case was presented at the November 1957 staff meeting of the Birmingham Baptist Hospital. It created so much discussion that I was hopeful I would learn something here. I would like to suggest that he had what Conn[2] and others have called "secondary aldosteronism". It has been shown by several different workers, such as Dyrenfurth[3], that there is a marked increase in aldosterone excretion up to 6 times normal in patients suffering from portal cirrhosis. I would appreciate comments as to whether in certain selected cases this increase can be of such degree as to put a patient into heart failure. Conn has stated that patients with

primary aldosteronism with a functioning tumor of the adrenal cortex do not have edema. Aldosterone is noted in the urine in excessive amounts in edematous nephrotics, cardiacs with congestive heart failure, patients with decompensated cirrhosis and women with eclampsia. Conn feels that it is reasonable to assume that in the course of development of each of these conditions, a common metabolic event occurs which triggers the production of excessive quantities of aldosterone. This he calls "secondary aldosteronism". So I believe that Drs. McHardy and Watkinson came very close to the explanation of this man's difficulties.

In summary, this patient developed serum hepatitis which progressed to postnecrotic cirrhosis. The only explanation I have is that we must postulate that some metabolic disturbance occurred in the liver for a period of at least six months, causing marked salt and water retention, hypertension and heart failure. I would say that this would probably be secondary aldosteronism.

Dr. Hertzog:—Gentlemen, that's the diagnosis. I would like to have some comment as to whether you agree or don't agree with it.

Dr. Murrel H. Kaplan:—The study of the adrenal glands as most of us know, particularly the *zona glomerulosa* is just getting under way. I offer this as a suggestion. We are very well aware at times of thyroid crises. I wonder if there is, though I have not seen it in the literature, an aldosterone crisis; and that the type of heart disease seen here is a reversible type, much like we see in thyroid crises. Now I don't know that there is any way of proving it, but certainly the suggestion here is one of tremendous peripheral vasoconstriction inasmuch as the arterioles of the eye seem to be in spasm, and the tumor of the adrenal cortex, as Dr. Watkinson has said, would maintain a persistent blood pressure whereas this might represent some type of temporary hyperplastic phenomena, or hyperactivity phenomenon much like we see in hyperthyroidism. I throw that out for what it's worth and you may throw it out completely.

Question:—What is the evidence for congestive failure?

Dr. Manuel Gardberg:—Unsolicited I would have nothing to say about this. This brings up the question of the definition of congestive heart failure, and I think we could talk about that for quite a long time and probably not get too far. But let us say the man had the syndrome of generalized edema and symptoms that are generally associated with congestive heart failure, but which also occur in other conditions, such as nephrosis and so on. Rather than to get into this argument as to whether this man had congestive failure or not, I would just like to point out that the association of this picture with liver disease is really not new. Under various names and under various conditions the association of a generalized edema and fluid in the chest, etc., with liver disease has been known and described before; and we know that in some instances it is

associated with conditions that are supposed to be primary in the kidneys—in eclampsia and obstetrical complications. The notion of the hepatorenal syndrome was invoked and has some merit in explaining the combination of such findings as we have here except that in this case there was no evidence of renal disease. In some cases of liver disease, 20 or 25 years ago when we saw a good deal of syphilis and especially congenital syphilis, there were a fair number of cases that had generalized anasarca, associated with syphilis of the liver and no other lesion to explain it; here again there was invoked this notion of some sort of hepatic influence on the circulatory system and renal system even in the absence of any demonstrable renal lesion in the clinical picture. Now that doesn't explain too much except that I think that possibly something can happen in the liver which I believe has been demonstrated before, that can affect the excretion of fluid and electrolytes and perhaps aldosterone excretion in high amounts. It seems as if that could be checked in some cases. The general concept is not new that liver disease can affect the functions of electrolyte and fluid control and produce a picture that is similar to that of congestive failure.

Dr. Philip Tiller:—There isn't too strong evidence for generalized edema. He had two plus edema at most in his legs, fluid in the abdomen later on, and fluid in his chest. He coughed up blood for 3 months before the onset of dyspnea and edema. In these circumstances, the obvious consideration ought to be thrombophlebitis with showers of emboli to the chest.

Dr. Hertzog:—Dr. McHardy, would you like to make any closing statements?

Dr. McHardy:—The closing statement should be "don't overlook the obvious". It was quite obvious to all that this was serum hepatitis to begin with. It seems we should have been able to follow right down the line and conclude that this person did have, as Dr. Davis suggested, a progression to a postnecrotic cirrhosis. There is the story and I think that concludes it pretty nicely. I think that we were misled probably concerning his congestive heart failure; the opinion of the cardiologist left you with the impression that he did have heart failure on some other basis. I failed to note he actually was saying that this man did not have heart disease or heart failure which apparently is the conclusion.

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TREATMENT OF VASCULAR HEADACHE WHEN ACCOMPANIED BY NAUSEA AND VOMITING

Preliminary Report

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"Headache is a symptom that few, if any, mortals have never experienced"[1]. It is, in fact, probably the most frequent of all complaints encountered in practice. Ogden has reported that the incidence of recurrent headache in a group of 4,634 patients was greater than 64 per cent (3,005 subjects)[2]. Other authorities have indicated that the most common form of vascular headache—migraine—is responsible for 8 to 12 per cent of all the patients seen in general practice[3,5]. Many of these migraine patients, unfortunately, present not only the "classical" signs of the syndrome, i.e., prodromal visual disturbances, unilateral head pain of a throbbing nature, etc., but also a disproportionate amount of nausea and vomiting. This, however, is usually lacking in cases of histamine cephalalgia; thus, providing a valuable clue to the accurate differential diagnosis of migraine from other vascular headaches.

When the migraine type of vascular headache attack is complicated by episodes of nausea and vomiting, alleviation of the symptoms may not always be practicable by means of oral medication. The purpose of this report is to present a method of treatment for those patients whose headache attacks are marked by severe nausea and vomiting, making oral medication difficult, and in whom parenteral therapy is not always practical.

The preparation used in this series was a *rectal* suppository* containing the following ingredients in a vegetable oil base: ergotamine tartrate (1.0 mg.); caffeine (100.0 mg.); l-belladonna alkaloids (0.1 mg.); and acetophenetidin (130.0 mg.).

Case Reports

The first case report illustrates the importance of controlling nausea in migraine, especially when it is a prominent feature of the syndrome:

Case 1:—A. B., female, age 65, housewife. Good general health. First seen by me 15 years ago. She complained of severe throbbing head pain which occurred usually during the early morning hours (4:00 a.m.) and which lasted from 6 to 48 hours without abatement. When awakened she would be so nauseous that she was unable to take any medication by mouth and was too upset emotionally to administer a hypodermic injection. A suppository containing ergotamine and caffeine in a cocoa butter base had been used but it had

*Wigraine®, Organon Inc., Orange, N. J.

afforded her little relief. In fact, it had actually increased her nausea (seemingly due to its slow onset of therapeutic effect, which upset her to the point where she was unable to resume sleep). Her past history indicated that the onset of her migraine attacks coincided with her menstrual periods during her teenage. In the period of her menopause these attacks increased both in frequency and in severity. For two years following her menopause she was free from headaches. Later, they recurred when she was subjected to a great deal of stress and emotional upset. Thus, she has had migraine during her premenopausal, menopausal, and postmenopausal periods, with her attacks being "triggered" by emotional upsets resulting from family and marital problems. (In her late thirties she was hospitalized for a so-called nervous breakdown; during this period she experienced depression, but few headaches.) Since it was not possible to remove the causative agent for her headaches, Wigraine suppositories were prescribed for symptomatic relief. Rapid relief (10-15 minutes) of head pain was obtained; but, more important, relief of vomiting occurred without excitation and before she became too upset to resume sleep. This striking relief of nausea and vomiting afforded the patient by Wigraine is no doubt due to its reduced ergotamine tartrate content (1.0 mg.)—about one-half that of her previous medication. Although Wigraine contains belladonna to relieve nausea, its rapid onset of effect terminates the attack before it reaches the point where nausea and vomiting are no longer reversible. Her occasional daytime migraine attacks have been well-controlled with Wigraine tablets when taken before nausea makes any oral medication impossible.

The importance of rapid-acting therapy—plus relief of associated muscle pain—is demonstrated by the next case report:

Case 2:—A. C., male, age 58, chemist. Good general health. When seen, patient complained of severe, throbbing head pain of 20-minute to two-hour duration. The pain usually awakened him from sleep; however, it sometimes also occurred during the early evening hours—but never during his working hours. Past history revealed "sick headaches" were present during his college period. The intensity and frequency of headaches was greater during examination periods and particularly during his senior year. These headaches gradually decreased in severity and intensity after leaving college. The present headaches began at approximately the age of 50, following a stressful period at work. They appeared sporadically and in clusters (two or three times during a 24-hour period), and then not for several weeks or months. At the time that the patient was seen by the writer, the headaches had increased in intensity and frequency so that they were now almost constantly with him, thus interfering with sleep and affecting his work. The latter headaches differed from "sick headaches" in that they were much more severe, of shorter duration, and of sudden onset. This was in contrast to the slow, gradual onset of the previous headaches which also had a longer duration (two to three days). Residual soreness of the neck, tearing of the eyes, and some nasal stuffiness was present. Diagnosis of hista-

mine cephalalgia or Horton's syndrome was made. Since his headaches came on shortly after falling asleep, one Wigraine suppository was prescribed to be taken shortly before going to bed. Favorable results followed this regimen and the medication was continued nightly for two months. Since Wigraine, or any other ergotamine preparation is not indicated for continuous administration, medication was discontinued upon disappearance of symptoms. If, however, his headaches should recur, Wigraine suppositories will again be prescribed. The patient is now taking a nonbarbiturate sedative nightly for his insomnia, which still persists to a slight degree.

The third case report, a histamine cephalalgia patient, again illustrates the need for fast-acting medication, plus, in this particular instance, a nonirritating rectal suppository:

Case 3:—A. D., male, age 54, physician. Good general health. First seen in January, 1954, complaining of sinus trouble with associated intense pain of very short duration over medial aspect of left front orbital area. Past history revealed no headaches prior to age 50. Along with the head pain, the patient also complained of nasal congestion, which had been previously diagnosed as an allergic reaction with sinus blocking. Further examination and observations made during an actual attack, revealed the headaches to be histamine cephalalgia. Conjunctival injection and tearing of the left eye and congestive obstruction of the mucous membrane of the left nostril and a tenacious thickening of the posterior nasal mucus preceded the headache, which was usually severe but of relatively short duration (20 minutes to 3 hours). The headaches occurred at the end of the working day, but occasionally were delayed long enough to occur during the night, thus awakening the patient. Wigraine rectal suppositories were prescribed, with relief being noted by the patient 10 to 15 minutes after taking one suppository. Speed of action with this preparation was quite important since the attacks were of short duration and, without the Wigraine, would cause considerable discomfort to the patient before termination. Previous rectal suppositories had not proven rapid enough in action and also had a tendency to produce rectal irritation. Wigraine rectal suppositories have been used for about a year by this patient, and thus far, have not caused any irritation or discomfort due to ingredients of base. With this base (Wecobee) only one suppository (1.0 mg. of ergotamine) was needed to abort an attack, whereas, with the previous medication with a cocoa butter base, 2 mg. of ergotamine were required. This reduction in ergotamine content is important particularly with a histamine cephalalgia patient, since frequency of attacks makes it necessary to repeat the medication often during a given week. The possibility of exceeding a weekly maximum for ergotamine is thus only half as great with this preparation than with tablets, as it took two to three tablets to obtain the equivalent relief of one Wigraine suppository when taken early during the onset of an attack. This patient had previously had a course of histamine desensitization without satisfactory relief of his headaches.

This next case is interesting in that it not only concerns atypical migraine, but that it also reflects a patient's changing attitude towards the use of rectal suppositories:

Case 4:—C. D., male, age 22, biochemist. First seen in 1948 complaining of upset stomach associated with mild head pain. The diagnosis was atypical migraine. During the patient's teens the head pain became the predominant complaint and the nausea and vomiting secondary. During the college period, there was an increase in the frequency of headaches, particularly during examination periods when the patient experienced almost continual headaches and was required to take daily medication. Prodromal symptoms (warning "aura") have made oral medication possible, although on occasions medication was not taken early enough in the attack and headache of one to two days' duration resulted. Wigraine rectal suppositories were first prescribed for those occasions when the headache got out of control, making oral medication impossible; however, on one occasion when the patient's supply of tablets was depleted before a "full-blown" attack, Wigraine suppositories were substituted with excellent results. The patient was amazed at the ease and convenience of administering a suppository and has since continued to use them in preference to the oral tablets which, he felt, did not work as rapidly, nor provide as complete relief as the suppositories.

Rectal medication has not been readily accepted initially by the majority of patients seen in my practice, but once tried, it has usually proven to be most acceptable. One must assure the patient that the suppository will not leak or soil clothing or bed sheets and may be inserted in any convenient bathroom. The patient described in Case 4 also demonstrates the ease with which Wigraine suppositories control the symptoms of migraine even after the attack has progressed. It has, however, been my experience with suppositories that once the attack is "full-blown", the dosage required to abort the attack may be twice the usual amount and on such occasions two suppositories inserted simultaneously produced excellent results without any undesirable side-effects.

Case 5 is a migraine patient of several years' duration who had also experienced a minor cerebral accident (which in no way affected the severity or frequency of the migraine headaches):

Case 5:—C. E., female, age 40. She complained of severe pain of the right side of her head with a left-sided hemiplegia with transient hemianopsia. Past history revealed migraine of several years' duration which always occurred on the left side of her head. Diagnosis was a small cerebral thrombosis of one of the branches of the middle cerebral artery on the right side of the head, and recurrent left-sided migraine. The pain from the cerebral thrombosis was severe and steady, in contrast to the throbbing type of pain experienced with her migraine attacks. Since the patient experienced minor difficulty in swallowing, Wigraine suppositories were prescribed for her migraine, which remained un-

affected by the cerebral accident. The analgesics and narcotics which were given to relieve the head pain associated with the cerebral vascular disease did not affect the mirgaine headache. Similarly, the Wigraine did not affect the pain resulting from the vascular disease, but did continue to relieve the head pain, nausea, and tension associated with her migraine attacks.

Comment

The above case reports were chosen from a series of ten patients under treatment for migraine headache. These patients were unanimous in noting not only more rapid relief of migraine with Wigraine than with any other medication, but also in attaining complete relief of the attack using a rectal suppository containing only one-half the amount of ergotamine necessary for effective oral medication.

The rapid action provided by Wigraine rectal suppositories (greater than that attained by oral tablet medication) may, perhaps, be attributed to its enhanced absorption through the rectal mucous membrane, which is a more direct and efficient entrée into the vascular system than via the upper gastrointestinal tract. Furthermore, this route eliminates possible reduction in activity due to the detoxification that would occur if it passed through the liver. The more rapid absorption via the rectal vascular system—without any loss of potency (by circumventing the liver)—allows for a reduction in the ergotamine content (1.0 mg.) to a level approaching that of one-half to three-quarters less than most patients with migraine would require if taken orally.

Summary

Five case histories have been presented which demonstrate the effectiveness of a new vascular headache preparation, "Wigraine rectal suppositories". A method of treatment has been suggested for those vascular headache patients who are unresponsive to oral medication and in whom parenteral therapy is not always practical. Wigraine suppositories were prescribed for these patients, with relief of head pain usually being noted within 10 to 15 minutes. Relief of head pain was, in all cases, accomplished without a concomittant increase in nausea, vomiting, and "jitteriness", due to the reduced ergotamine content of this preparation.

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CORRECTION OF CONSTIPATION IN SEVERELY INCAPACITATED INVALIDS AND IN PATIENTS WITH NEUROLOGIC DISEASES

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and

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In a chronic disease hospital constipation is a constant recurring problem to the patients, doctors, nurses and attendants. These patients present a difficult problem of cathartic administration. Because of their disabilities they are frequently bowel conscious and not amenable to reeducation of their bowel habits.

During the past few years, we have constantly evaluated various old and new constipation correctives. In this period it became evident that no one medication would be effective in all patients and all types of constipation. Improvements with some patients and failures in others occurred regardless of management. As an example, the prophylaxis of impaction and fecalomas, particularly in the debilitated patient was found to be possible. Straining, sphincter spasm, and irregularity of defecation, however, often could not be controlled despite adequate fecal hydration.

More recently we conducted an evaluation of a new senna preparation*. This preparation, which is available in the form of tablets and granules, is obtained by a special purification process from the de-seeded pod of *Cassia acutifolia*. It contains Sennosides A and B, plus as yet unidentified glycosides[1], the latter being synergistic to both the known sennosides. Although the entire activity is still not fully accounted for, this preparation is stable and lends itself, at present, to proper standardizations[2].

Previous pharmacological studies[1-7] have determined that the normal defecatory mechanism is re-established by the absorption of the senna principles into the blood stream from the small intestine (without affecting the motility pattern of the upper gastrointestinal tract), and the re-excretion of the inactive glycosides into the large bowel where they are converted by bacterial enzyme action into the active neurogenic principles which specifically stimulate Auerbach's plexus.

Materials and Methods

Forty-four severely ill chronic invalids were selected and comprised this study group in whom defecation was a constant serious concern to the staff as

From the Medical Department, The Jewish Chronic Disease Hospital, Brooklyn, N. Y.

*Senokot, supplied by The Purdue Frederick Company, New York, N. Y.

well as the patient. A study of our chart (Table I) indicates the difficult type of patient selected for this trial.

Of these 44 patients, 20 suffered from various forms of Parkinsonism in whom muscle rigidity and diminished motor power interfered with reflexes: of the others 9 had sustained at least one cerebrovascular accident, 4 suffered from multiple sclerosis with autonomic disturbances, 2 with *tabes dorsalis*, 4 with arteriosclerotic heart diseases, one each with transverse myelitis and para-

TABLE I

EFFECT OF TREATMENT WITH SENOKOT ON CONSTIPATION IN THE CHRONICALLY ILL, BEDRIDDEN PATIENT

No. of Cases	Diseases	Excellent	Good	Not Improved	Side-effects (Griping)
20	Parkinsonism	10	3	6	1
9	Cerebrovascular	4	2	2	1
4	Arteriosclerotic Heart Diseases	2		2	
4	Multiple Sclerosis	1		1	2
2	Cerebral Atrophy	1		1	
2	*Tabes Dorsalis*	1		1	
1	Encephalitis	1			
1	Paraplegia	1			
1	Rheumatoid Arthritis	1			
44		22	5	13*	4

*Ten of these patients noted improvements when psyllium was added to the senna medication.

plegia, rheumatoid arthritis, encephalitis, and 2 with cerebral atrophies. Each of these patients had been hospitalized for many years and were specially selected for this study, because of previous failures in bowel management, despite use of a large battery of laxative cathartics and enemata.

The dosage regimen employed was one level teaspoonful or 2 tablets once daily, increased gradually if necessary to a maximum dose of 2 level teaspoonfuls or 4 tablets twice daily until the minimum effective dose for maintenance of bowel regularity was attained. This was then either decreased or maintained as the results indicated.

In the second part of this study, the patients who did not benefit from the test preparation were placed on a regimen of the test preparation with psyllium. The dosage of the latter was one level teaspoonful (3 gm.) daily, equivalent to the total active constituents of 450 mg. of senna pods and 1 gm. of psyllium husks.

Results

The results were evaluated as follows, "Excellent", where bowel rehabilitation was achieved with stools of normal consistency. "Good", where bowel regularity and a physiologic urge was equal or superior to all previous medications without griping. "Not improved", if the condition remained *status quo.*

Of the 44 patients, 27 or 61 per cent achieved regular bowel movements on Senokot alone, 22 of the 27 had excellent results and 5 good results. (See Table I). Ten of the 13 patients who did not obtain significant improvement in bowel pattern with the test preparation alone, achieved excellent results with the addition of psyllium. The over all improvement of both parts of this study was achieved in 37 patients or 87 per cent of the total.

Mild griping was experienced on occasions in 4 patients. One patient with Parkinsonism had only a single impaction, whereas, he had previously suffered weekly impactions.

The following illustrates the beneficial effects of this senna preparation:

B.A. is a 34-year old white male with congenital brain lesion, right hemiparesis and convulsions, oxycephalus and right rotating scoliosis of the lumbar vertebra, who has been immobilized all his life. In spite of continuous use of various evacuants, the patient has been suffering from chronic constipation and impaction with frequent need for mechanical fecal dislodgement. This severe constipation must undoubtedly be ascribed to neurologic and autonomic imbalance, and the sedentary existence aggravated by phenobarbital and Dilantin which *per se*, produce marked obstipation. With 4 tablets of Senokot each evening, the patient has a formed stool, easily evacuated the next morning.

Comment

Among the many factors, responsible for constipation in institutionalized patients, such as psychologic or environmental factors, constipation medications, and bed rest, are the diseases of the nervous system. Disturbances in autonomic nervous system balance accompanied by abnormal reflex activity of any portion of the gastrointestinal tract may result in atony or localized spasm. Even in the less handicapped patient, this factor may be the commonest form of chronic constipation. The elderly, debilitated patient is particularly prone to these disturbances in the act of defecation, and to the development of dyschezia with loss of the defecation reflex. Yet even here, a considerable degree of

the normal function may be regained through stimulation of the intrinsic plexuses which exercise independent control. The senna preparations studied here seem to exert this stimulation satisfactorily, as demonstrated in the gratifyingly high percentage of our selected patients with severe constipation who responded well and were significantly relieved. A number of patients required the restoration of intraluminal pressure by the bulking action of psyllium plus the peristaltic stimulation of Senokot.

Conclusions

1. A series of 44 severely constipated chronically ill patients including many bedridden and paraplegics were studied for the corrective effects of Senokot and Senokot with psyllium on bowel motility.

2. On Senokot alone, 61 per cent sustained significant improvement and 29 per cent did not.

3. Seventy-six per cent of the latter achieved improvement on Senokot with psyllium.

4. Treatment of refractory constipation by this regimen in patients with severe neurological diseases was extremely beneficial.

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GASTRIC CANCER IN MEXICO*

PEDRO RAMOS, M.D., F.A.C.G.
REBECA W. DE ANGELES, M.D.
SERGIO MORENO, M.D.
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Mexico City, D.F.

This paper shows figures from different sources. It provides data from hospitals, a little different in social conditions. This fact adds interest to the figures presented.

The proportion of gastric cancer in relation to cancer in general is high, more than ten per cent, in the entire country.

We will show the percentage in a big general hospital, in a specialized service and in a hospital with many gastroenterological patients. We have been permitted to examine their records and in the Servicio de Gastroenterología, Prof. Dr. Abraham Ayala Gonzalez General Hospital, Mexico, D.F.

In these observations you will find the same similarities and differences as in the data provided from the United States.

TABLE I

100 CASES

Age	Hospital de Nutrición
Maximum	87 years
Minimum	28 years
Average	58.4
Less than 30 years	2 cases 2%
31-40	12 cases 12%
41-50	12 cases 12%
51-60	40 cases 40%
61-70	19 cases 19%
71-80	10 cases 10%
More than 80	5 cases 5%

A recent report from the General Hospital shows the results obtained in cytological examinations.

*Read before the Mexico Regional Meeting of the American College of Gastroenterology, Mexico, D.F., 27 October 1958.

Finally, we wish to remind you of the fact so well known now, among English and American investigators, i.e. the presence of group A in many cases of cancer of stomach in general and of the antrums in particular. Emphasis is placed on the different proportion found in Mexico.

TABLE II

LOCATION

1946-1957

	Hospital General
Upper half	49
Fornix	15
Lower third of the esophagus	8
Esophagogastric junction	23
Corpus and fornix	2
Cardiac neoplasm invasion to omentum, peritoneum and left ovary	1

TABLE III

LOCATION

	Hospital de Nutrición	
Antrum	45	45.4%
Corpus	16	16.1%
Greater part of the stomach	9	9.09%
Fornix	9	9.09%
Corpus and antrum	8	8.08%
Pylorus	3	3.03%
Esophagogastric junction	3	3.03%
Corpus and fornix	2	2.02%
Reinvasion (operated)	1	1.01%
Undetermined	3	3.03%
Total	99	

Group A is absent or almost absent in some Indian groups and they must have lowered the proportion of this blood group among "mestizo" population. (Most part of Mexican population is "mestizo", from Indian and European stock mixed during centuries).

Nevertheless cancer of the stomach is not uncommon as has been shown.

TABLE IV

SYMPTOMATOLOGY

100 CASES

	Hospital de Nutrición
Loss of weight	84%
Epigastric pain	82%
Dispeptic distress	69%
Asthenia	65%
Vomiting	53%
Anorexia	49%
Epigastric postprandial fullness	45%
Constipation	33%
Melena	28%
Hematemesis	23%
Palpable mass	17%
Diarrhea	14%
Fever	10%
Ascites	4%
Icterus	3%
Adenopathies	2%

TABLE V

CYTOLOGY*

Technic	Number of cases	Results Obtained			
		Pos.	Neg.	Doubt.	Insuf.
Abrasive balloon	76	22	43	9	2
Gastric lavage	6	2	2	1	1
Gastric aspiration	3	3			
Esophagic lavage	10	7	1		2
Total	95	34	46	10	5

*Hospital General Dr. Lilia Avila Ramírez.

President's Message

Hawaii Bound

I am sure that you will forgive me when I utilize this space to bring you some important information on our meeting in Hawaii.

As you know, we will adjourn the Convention in Los Angeles and reconvene in the 50th and newest State a few days later. This will be the first time that we are meeting outside of the continental United States.

The scientific sessions will be under the direction of our Secretary-General, Dr. Lynn A. Ferguson, who is charged with the running of regional meetings. I have seen copies of the correspondence between the Islands and the Mainland and you can be sure that the program will be of a very high calibre.

Final arrangements for the sessions will be made in Atlantic City during the AMA Convention, when one of the doctors from Hawaii will meet with us.

You have all received the colorful brochures giving in detail the facts about the wonderful trip. Many of you have already expressed a desire to be included in the group which is flying from Los Angeles to Honolulu. From all indications, a good many of our membership will take advantage of this opportunity to learn at first hand what is being done in gastroenterology in Hawaii. Several of the membershp will participate in the program and present what we are doing in this field.

To make this a successful program, if you have not already made your reservations for Los Angeles and Hawaii, may I suggest that you do so at once. I hope that I shall have the privilege and honor of greeting you there.

Frank J. Borrelli

In Memoriam

We record with profound sorrow the passing of Dr. Ernest Springer of Boston, Mass., Member and Dr. Frank A. Cummings, Providence, R. I., Life Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

To the Editor:

Dr. Joseph Shaiken's article: "Duodenal Ulcer in Children" which was read at the 23rd Annual Convention of the American College of Gastroenterology in New Orleans in October 1958 has been published in the February 1959 issue of The American Journal of Gastroenterology. His article is of great interest.

Dr. Shaiken has apparently missed the two articles concerning my own studies of peptic ulcers in children, since these were not mentioned. The first paper, which was published in The American Journal of Gastroenterology of June 1955 was entitled "Roentgenological Studies of Gastric Secretion in Children." The second has the title of "Roentgenological Findings in Gastric Duodenal Ulcers in Children" and has been published in the July 1955 issue of the American Journal of Digestive Diseases (**22**:189-194). Therefore, Dr. Shaiken's remark in the discussion on page 139 of this Journal that "no articles in journals of any national level have been published" is incorrect. I feel very sorry that Dr. Shaiken overlooked my publications which reported the findings in much younger children.

New York, N. Y. Franz J. Lust, M.D., F.A.C.G.

To the Editor:

The comment made in the discussion was not intended to ignore previous publications. As I stated there were approximately 35 papers available for review of this subject in the last few years.

I merely intended to convey that discussions concerned with the complete clinical presentation of peptic ulcer in children were singularly lacking in national periodicals. Most of these papers were either single case reports or limited to some phase of the subject.

The two above mentioned papers fall into this category.

Milwaukee, Wisc. Joseph Shaiken, M.D., F.A.C.G.

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1. Bandes, J.: Combined Drug Therapy in Gastrointestinal Disturbances; Increased benefit through diminished side reactions, Am. J. Gastroenterology, *30*:600, Dec. 1958.

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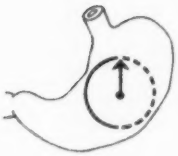

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[1] *American Journal of Gastroenterology* 28:439, 1957.

[2] *British Medical Journal* 2:827, 1955.

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SUMMARY OF CASES

Clinical Diagnosis	*Oxyphencyclimine[1,3,5,6]	†ENARAX[2,3]
Peptic ulcer	440	48
Gastritis	16	17
Gastroenteritis	—	55
Colitis	37	—
Duodenitis	6	3
Functional bowel syndrome	14	—
Hiatus hernia (symptomatic)	16	1
Pylorospasm or cardiospasm	11	2
Irritable bowel	11	—
Biliary tract dysfunctions	11	1
Miscellaneous	7	29
Total number of patients	569	156
Clinical Results *Excellent*	445	150
Fair	56	—
Failure	68	6

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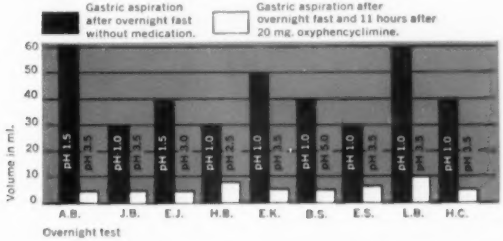
ACID REDUCTION AFTER OXYPHENCYCLIMINE THERAPY

Tests conducted in 9 representative ulcer patients after overnight fasts showed considerable reduction in both volume and acidity.



References: 1. Winkelstein, A.: Am. J. Gastroenterol., in press. 2. Leming, B. H., Jr.: Clin. Med. *6*:423 (March) 1959. 3. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, Calif., January 27, 1958. 4. Straub, I. H., and Carballo, A.: To be published. 5. Data in Roerig Medical Department files. 6. Steigmann, F.: To be published. 7. Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1957. 8. Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. 9. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957.

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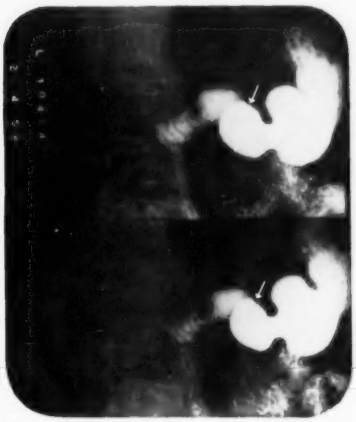
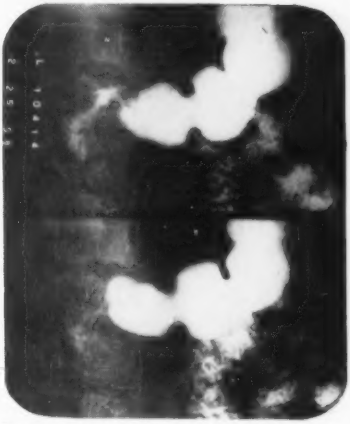
relieve the tension

—and control its G.I. sequelae



Patient A.S., age 53.
Intermittent crises of severe pain over 2 year period: hospital management with Sippy regimen provided relief of symptoms: however, symptoms recurred after each sojourn.



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Duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility.

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Bottles of 100 and 1,000. Each tablet (yellow, ½-scored) contains Meprobamate, 400 mg.; PATHILON Tridihexethyl Chloride, 25 mg.

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Atropine sulfate	0.0194 mg.	0.0582 mg.
Hyoscine hydrobromide	0.0065 mg.	0.0195 mg.
Phenobarbital	(¼ gr.) 16.2 mg.	(¾ gr.) 48.6 mg.

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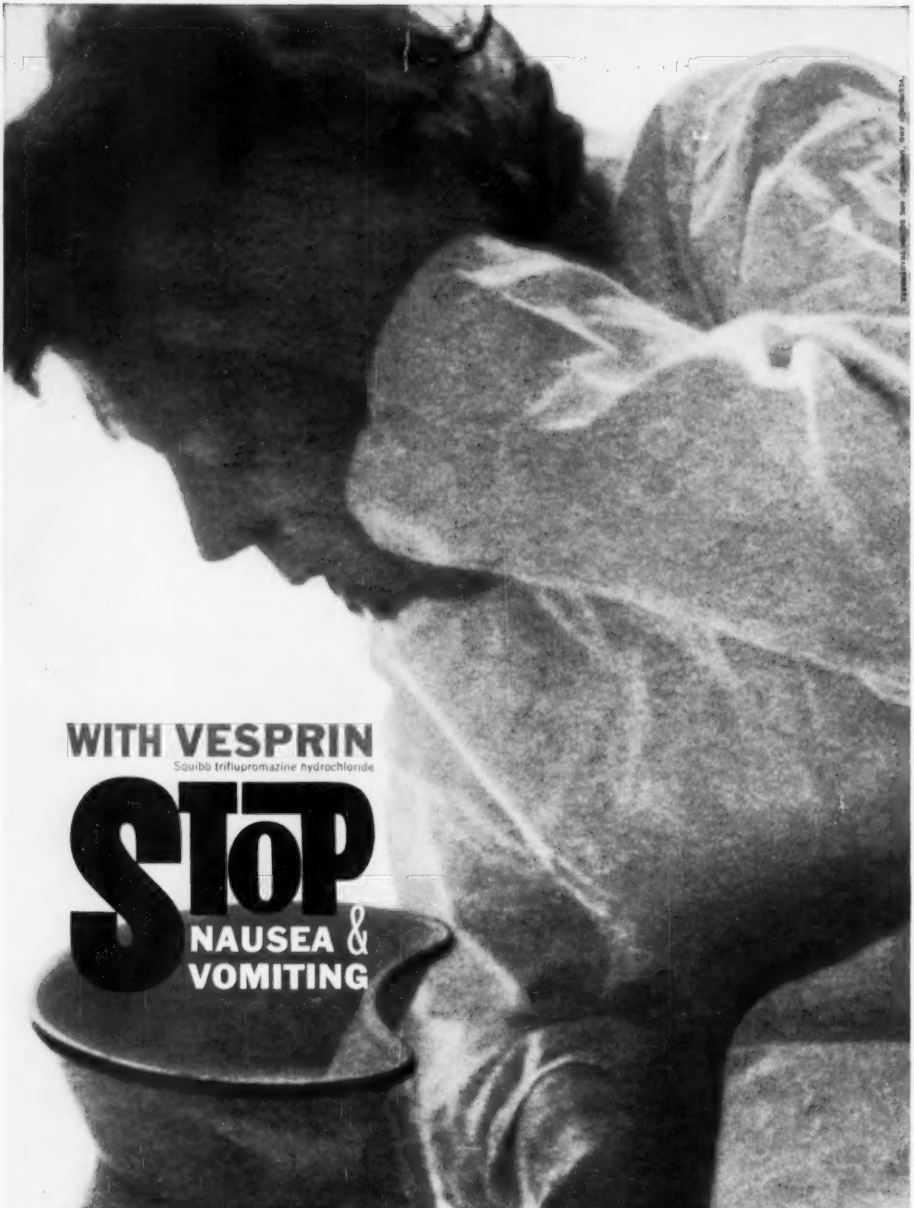

Dosage: Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

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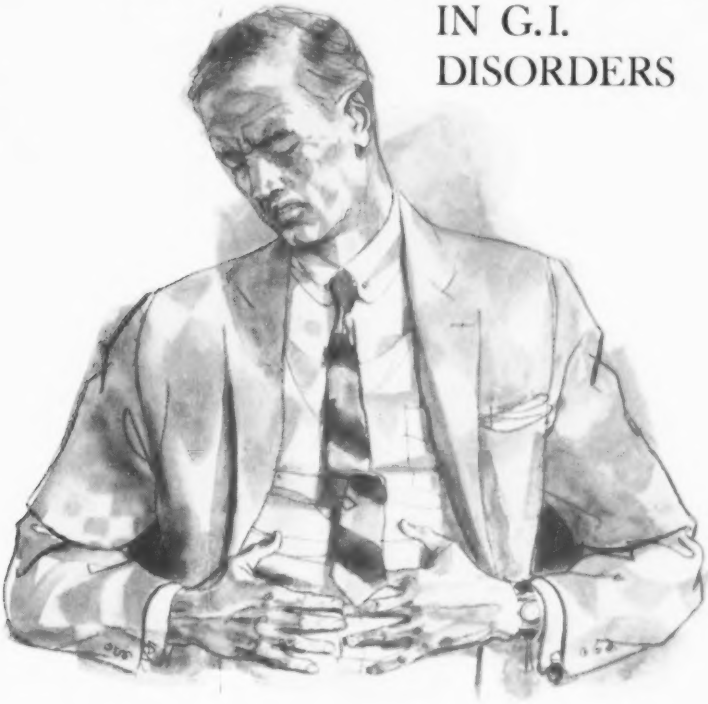

MOST FUNCTIONAL G.I. DISORDERS "can be considered a manifestation of a general psychoneurotic disturbance." (Rossien, A. X.: J. Am. Geriatrics Soc. 5:430, April 1957.)

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1. Phillips, R. E.: Am. Pract. & Digest Treat. 7:1573, Oct. 1956. 2. Selling, L. S.: J.A.M.A. 157:1594, April 30, 1955. 3. Altschul, A. and Billow, B.: New York J. Med. 57:2361, July 15, 1957. 4. Ross, S. T.: Postgrad. Med. 23:24, Jan. 1958. 5. Tacket, H. S.: Am. Pract. & Digest Treat. 8:597, April 1957. 6. Bodi, T., Wirts, C. W., Jr. and Menduke, H.: Am. J. Gastroenterol. 29:643, June 1958.

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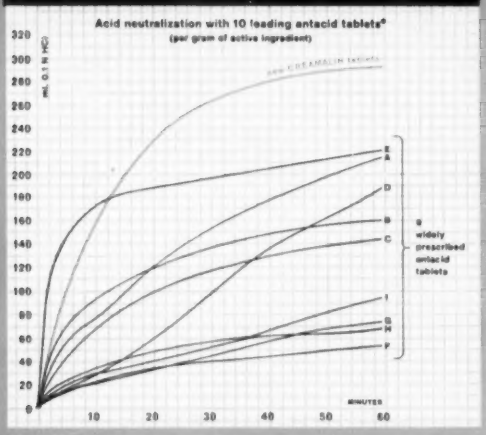

Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

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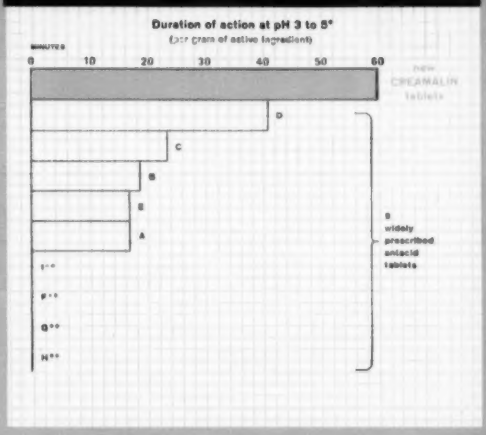

*Hinkel, E. T., Jr., Fisher, M. P. and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.

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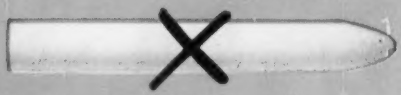

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